オプジーボ点滴静注 20mg
オプジーボ点滴静注 100mg
オプジーボ点滴静注 120mg
オプジーボ点滴静注 240mg
に関する資料

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小野薬品工業株式会社

1.5 起原又は発見の経緯及び開発の経緯

小野薬品工業株式会社

ブリストル・マイヤーズ スクイブ株式会社

1.5　起原又は発見の経緯及び開発の経緯

本製造販売承認事項一部変更承認申請（以下、本一変申請）にかかる開発の経緯を表 1.5-1 に示した。

開発の経緯を除く当該内容については、［2.5.1］参照。

表 1.5-1　開発の経緯（今回の申請パッケージ）

試験項目			実施会社		2014 年	2015 年	2016 年	2017 年	2018 年	2019 年	2020 年	2021 年	2022 年	2023 年	2024 年
			小野薬品	BMS											
臨床（国際共同）	第Ⅲ相	ONO-4538-87 /CA2098HW 試験	●	●						⑧				⑩	⑥
臨床（海外）	第Ⅱ相	CA209142 試験（コホート 3）		●	③	■	■	■	■	■	■	■	■	■	⑥
臨床（海外）	第Ⅱ相	CA209142 試験（c ステージ）		●	③			⑦	■	■	■	■	■	■	⑥

小野薬品：小野薬品工業株式会社、BMS：Bristol-Myers Squibb Company、コホート 3：未治療の高頻度マイクロサテライト不安定性（MSI-High）又はミスマッチ修復機構欠損（dMMR）を有する結腸・直腸がん患者を対象としたニボルマブとイピリムマブの併用療法のコホート、c ステージ：既治療の MSI-High 又は dMMR を有する結腸・直腸がん患者を対象としたニボルマブとイピリムマブの併用療法のコホート

囲み数値は、左から順に治験開始月、臨床データカットオフ月及び本一変申請月を表す。ただし、c ステージでは治験開始月、1 回目の臨床データカットオフ月、2 回目の臨床データカットオフ月及び本一変申請月を表す。

1.6 外国における使用状況等に関する資料

小野薬品工業株式会社

1.6.1 外国における使用状況

ニボルマブ（遺伝子組換え）（以下、ニボルマブ）は、世界に先駆けて日本で 2014 年 7 月に製造販売承認されて以降、2025 年 5 月時点で日本及び欧米等 6 カ国（米・英・独・仏・加・豪）を含む 65 以上の国又は地域において複数の適応で承認されている。

高頻度マイクロサテライト不安定性（MSI-High）又はミスマッチ修復機構欠損（dMMR）を有する治癒切除不能な進行・再発の結腸・直腸がん（以下、CRC）に対するニボルマブ静注の主要な既承認国として米国及び EU における承認状況を表 1.6.1-1 に示した。一次治療の MSI-High 又は dMMR を有する CRC の治療薬として、ニボルマブとイピリムマブ（遺伝子組換え）の併用療法が米国では 2025 年 4 月に、EU では 2024 年 12 月に承認されている。米国添付文書及び欧州添付文書の原文を添付し、それぞれの概要を表 1.6.1-2 及び表 1.6.1-3 に示した。

表 1.6.1-1　MSI-High 又は dMMR を有する CRC に対するニボルマブ静注の主要な既承認国（米国及び EU）における承認状況

国名	販売名、剤形及び含量	承認年月日	効能又は効果	用法及び用量
米国	OPDIVO® (nivolumab) injection, for intravenous use 水溶性注射剤：1 バイアル中 40 mg/4 mL（10 mg/mL）、100 mg/10 mL（10 mg/mL）、120 mg/12 mL（10 mg/mL）又は 240 mg/24 mL（10 mg/mL）	2017 年 7 月 31 日	OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.	【単剤療法】 Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks* or 480 mg every 4 weeks* Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks* *: 30-minute intravenous infusion Until disease progression or unacceptable toxicity
		2018 年 7 月 10 日		【イピリムマブとの併用療法】 3 mg/kg every 3 weeks* with ipilimumab 1 mg/kg intravenously* In combination with ipilimumab for 4 doses Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks* or 480 mg every 4 weeks* Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks* After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity *: 30-minute intravenous infusion on the same day
		2025 年 4 月 8 日	• OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). • OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine,	【イピリムマブとの併用療法】 Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 3 weeks* with ipilimumab 1 mg/kg* Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 3 weeks* with ipilimumab 1 mg/kg* In combination with ipilimumab for a maximum of 4 doses Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks*

			oxaliplatin, and irinotecan.	or 480 mg every 4 weeks* Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks* After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity, or up to 2 years * 30-minute intravenous infusion on the same day. 【単剤療法】 Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks* or 480 mg every 4 weeks* Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks* Until disease progression or unacceptable toxicity * 30-minute intravenous infusion.
EU[a)]	OPDIVO® 10 mg/mL concentrate for solution for infusion 水溶性注射剤： 1 バイアル中 40 mg/4 mL（10 mg/mL）、 100 mg/10 mL（10 mg/mL）、 120 mg/12 mL（10 mg/mL）又は 240 mg/24 mL（10 mg/mL）	2021 年 6 月 24 日	OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.	3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at 240 mg every 2 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks.
		2024 年 12 月 19 日	OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings: – first-line treatment of unresectable or metastatic colorectal cancer; – treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.	The recommended dose for first-line treatment of dMMR or MSI-H CRC is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab. Treatment with nivolumab is recommended until disease

				progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose in patients who received prior fluoropyrimidine-based combination chemotherapy for dMMR or MSI-H CRC is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab monotherapy administered intravenously 240 mg every 2 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab.

a）中央承認審査方式により承認

表 1.6.1-2　米国添付文書の概要

国名	米国
販売名	OPDIVO (nivolumab) injection, for intravenous use
会社名	Bristol-Myers Squibb Company（Princeton、NJ 08543 USA）
一般的名称	ニボルマブ
承認年月日	2014 年 12 月 22 日
剤形・含量	注射剤：単回使用バイアル入り 40 mg/4 mL（10 mg/mL）、100 mg/10 mL（10 mg/mL）、 120 mg/12 mL（10 mg/mL）及び 240 mg/24 mL（10 mg/mL）溶液
効能・効果	**1.1 切除不能又は転移性悪性黒色腫** OPDIVO®（ニボルマブ）は、切除不能又は転移性悪性黒色腫の成人患者及び 12 歳以上の小児患者に対する単剤療法又はイピリムマブとの併用療法を適応とする。 **1.2 悪性黒色腫に対する術後補助療法** OPDIVO は、根治切除後の IIB 期、IIC 期、III 期又は IV 期の悪性黒色腫の成人患者及び 12 歳以上の小児患者に対する術後補助療法を適応とする。 **1.3 切除可能な非小細胞肺がんに対する術前補助療法** OPDIVO は、切除可能（4 cm 以上の腫瘍又はリンパ節転移陽性）な非小細胞肺がん（NSCLC）の成人患者において、プラチナダブレット化学療法との併用療法での術前補助療法を適応とする。 **1.4 切除可能な非小細胞肺がんに対する術前及び術後補助療法** OPDIVO は、切除可能（4 cm 以上の腫瘍又はリンパ節転移陽性）な NSCLC を有し、上皮成長因子受容体（EGFR）遺伝子変異陰性又は未分化リンパ腫キナーゼ（ALK）融合遺伝子の再構成を伴わない成人患者において、プラチナダブレット化学療法との併用療法での術前補助療法と、それに続く術後の OPDIVO 単剤療法による術後補助療法を適応とする。 **1.5 転移性非小細胞肺がん** ・OPDIVO は、EGFR 又は ALK 遺伝子変異陰性で、FDA が承認した検査法*［用法・用量（2.1）参照］*で PD-L1 の発現が 1%以上認められた NSCLC の成人患者において、イピリムマブとの併用療法での一次治療を適応とする。 ・OPDIVO は、EGFR 又は ALK 遺伝子変異陰性の転移性又は再発性 NSCLC の成人患者において、イピリムマブ及びプラチナダブレット化学療法 2 サイクルとの併用療法での一次治療を適応とする。 ・OPDIVO は、プラチナ製剤を含む化学療法による治療中又は治療後に進行が認められた転移性 NSCLC の成人患者に対する治療を適応とする。EGFR 又は ALK 遺伝子変異を有する患者では、OPDIVO 投与前にこのような変異に対する FDA 承認を受けた療法で病勢進行が認められていることが必要である。 **1.6 悪性胸膜中皮腫** OPDIVO は、切除不能な悪性胸膜中皮腫の成人患者において、イピリムマブとの併用療法での一次治療を適応とする。 **1.7 進行性腎細胞がん** ・OPDIVO は、intermediate 又は poor リスクの進行性 RCC の成人患者において、イピリムマブとの併用療法での一次治療を適応とする。 ・OPDIVO は、未治療の進行性 RCC の成人患者において、カボザンチニブとの併用療法での一次治療を適応とする。 ・OPDIVO は、血管新生阻害剤による治療歴を有する進行性腎細胞がん（RCC）の成人患者に対する単剤療法を適応とする。 **1.8 古典的ホジキンリンパ腫** OPDIVO は、以下の治療後に再発又は進行した成人の古典的ホジキンリンパ腫（cHL）患者に対する治療を適応とする。 ・自家造血幹細胞移植（HSCT）及び移植後のブレンツキシマブ ベドチン、又は ・自家 HSCT を含む 3 次治療以上の全身療法 この適応は、全奏効率に基づき迅速承認制度下で承認された*［臨床試験（14.7）参照］*。この適応の承認の継続条件は、検証的試験において臨床的有用性を証明し、記載することである。 **1.9 頭頸部扁平上皮がん** OPDIVO は、プラチナ製剤を含む化学療法による治療中又は治療後に病勢進行が認められた再発又は転移性頭頸部扁平上皮がん（SCCHN）の成人患者に対する治療を適応とする。

	1.10 尿路上皮がん OPDIVO は、尿路上皮がん（UC）の根治的切除後に再発リスクの高い成人患者に対する術後補助療法を適応とする*［臨床試験（14.9）参照］*。 OPDIVO は、切除不能又は転移性尿路上皮がんの成人患者において、シスプラチン及びゲムシタビンとの併用療法での一次治療を適応とする。 OPDIVO は、以下の局所進行又は転移性尿路上皮がんの成人患者に対する治療を適応とする。 ・プラチナ製剤を含む化学療法による治療中又は治療後に病勢進行した患者 ・プラチナ製剤を含む化学療法による術前又は術後補助療法から 12 カ月以内に病勢進行した患者 **1.11 高頻度マイクロサテライト不安定性又はミスマッチ修復機構欠損を有する転移性結腸・直腸がん** ・OPDIVO は、切除不能又は転移性高頻度マイクロサテライト不安定性（MSI-H）又はミスマッチ修復機構欠損（dMMR）を有する結腸・直腸がん（CRC）の成人患者及び 12 歳以上の小児患者に対するイピリムマブとの併用療法を適応とする。 ・OPDIVO は、フルオロピリミジン、オキサリプラチン及びイリノテカンによる治療後に病勢進行した高頻度マイクロサテライト不安定性（MSI-H）又はミスマッチ修復機構欠損（dMMR）を有する転移性結腸・直腸がん（CRC）の成人患者及び 12 歳以上の小児患者に対する単剤療法を適応とする。 **1.12 肝細胞がん** ・OPDIVO は、切除不能又は転移性肝細胞がん（HCC）の成人患者において、イピリムマブとの併用療法での一次療法を適応とする。 ・OPDIVO は、ソラフェニブによる治療歴を有する切除不能又は転移性 HCC の成人患者において、イピリムマブとの併用療法を適応とする。 **1.13 食道がん** ・OPDIVO は、術前補助化学放射線療法（CRT）を受けた成人患者において、完全切除術後に病理学的残存病変を有する食道がん又は食道胃接合部がんに対する術後補助療法を適応とする。 ・OPDIVO は、PD-L1 の発現が 1 以上認められた*［用法・用量（2.1）参照］*切除不能な進行、再発又は転移性の食道扁平上皮がん（ESCC）の成人患者に対するフルオロピリミジン及びプラチナ製剤を含む化学療法との併用療法での一次治療を適応とする。 ・OPDIVO は、PD-L1 の発現が 1 以上認められた*［用法・用量（2.1）参照］*切除不能な進行、再発又は転移性の食道扁平上皮がん（ESCC）の成人患者に対するイピリムマブとの併用療法での一次治療を適応とする。 ・OPDIVO は、フルオロピリミジン及びプラチナ製剤を含む化学療法による前治療を受けた切除不能な進行、再発又は転移性の食道扁平上皮がん（ESCC）の成人患者に対する治療を適応とする。 **1.14 胃がん、食道胃接合部がん及び食道腺がん** OPDIVO は、PD-L1 の発現が 1 以上認められた*［用法・用量（2.1）参照］*進行又は転移性の胃がん、食道胃接合部がん及び食道腺がんの成人患者に対するフルオロピリミジン及びプラチナ製剤を含む化学療法との併用療法を適応とする。
用法・用量	**2.1 患者選択** 患者選択のための FDA が承認した検査に関する情報は、以下で入手可能である。 https://www.fda.gov/CompanionDiagnostics <u>非小細胞肺がん</u> ・OPDIVO をイピリムマブと併用して転移性 NSCLC 患者を治療する場合は、PD-L1 の発現状態に基づいて患者を選択すること*［臨床試験（14.5）参照］*。 <u>食道がん</u> ・OPDIVO をフルオロピリミジン及びプラチナ製剤を含む化学療法と併用して切除不能な進行、再発又は転移性の ESCC 患者を治療する場合は、PD-L1 の発現状態に基づいて患者を選択すること*［臨床試験（14.13）参照］*。 ・OPDIVO をイピリムマブと併用して切除不能な進行、再発又は転移性の ESCC 患者を治療する場合は、PD-L1 の発現状態に基づいて患者を選択すること*［臨床試験（14.13）参照］*。 ・進行、再発又は転移性の ESCC 患者における PD-L1 の発現状態を検出するための FDA 承認済みのコンパニオン診断薬はない。 <u>胃がん、食道胃接合部がん及び食道腺がん</u> ・OPDIVO をフルオロピリミジン及びプラチナ製剤を含む化学療法と併用して進行又は転移性の胃がん、食道胃接合部がん及び食道腺がん患者を治療する場合は、PD-L1 の発現状態に基づいて患者を選択すること*［臨床試験（14.14）参照］*。 ・進行又は転移性の胃がん、食道胃接合部がん及び食道腺がん患者における PD-L1 の発現状態を検出するための FDA 承認済みのコンパニオン診断薬はない。

2.2 推奨用量

単剤療法における OPDIVO 静注の推奨用量を表 1 に示す。
OPDIVO は 30 分かけて点滴静注する［*用法・用量（2.4）参照*］。

表 1　単剤療法における OPDIVO 静注の推奨用量

適応	OPDIVO の推奨用量	治療期間
転移性非小細胞肺がん 進行性腎細胞がん 古典的ホジキンリンパ腫 頭頸部扁平上皮がん 局所進行又は転移性尿路上皮がん 食道扁平上皮がん	240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔	病勢進行又は許容できない毒性出現まで
切除不能又は転移性悪性黒色腫	成人及び 12 歳以上の小児で体重 40 kg 以上： 240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔 12 歳以上の小児で体重 40 kg 未満： 3 mg/kg を 2 週間間隔 又は 6 mg/kg を 4 週間間隔	病勢進行又は許容できない毒性出現まで
悪性黒色腫に対する術後補助療法	成人及び 12 歳以上の小児で体重 40 kg 以上： 240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔 12 歳以上の小児で体重 40 kg 未満： 3 mg/kg を 2 週間間隔 又は 6 mg/kg を 4 週間間隔	疾患の再発又は許容できない毒性出現まで 投与期間は最大 1 年間
尿路上皮がん（UC）に対する術後補助療法	240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔	疾患の再発又は許容できない毒性出現まで 投与期間は最大 1 年間
転移性疾患に対する前治療による治療後に病勢進行した高頻度マイクロサテライト不安定性（MSI-H）又はミスマッチ修復機構欠損（dMMR）を有する転移性結腸・直腸がん	成人及び 12 歳以上の小児で体重 40 kg 以上： 240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔 12 歳以上の小児で体重 40 kg 未満： 3 mg/kg を 2 週間間隔	病勢進行又は許容できない毒性出現まで
切除後食道がん又は食道胃接合部がんに対する術後補助療法	240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔	病勢進行又は許容できない毒性出現まで最長 1 年間

他の治療薬との併用療法における OPDIVO の推奨用量を表 2 に示す。OPDIVO は他の治療薬と同日に投与すること。
OPDIVO と併用する治療薬の推奨用量については、それぞれの治療薬の添付文書を適宜参照すること。

表 2　他の治療薬との併用療法における OPDIVO 静注の推奨用量

適応	OPDIVO の推奨用量	治療期間
切除不能又は転移性悪性黒色腫	1 mg/kg を 3 週間間隔 イピリムマブ 3 mg/kg	イピリムマブとの併用は最大 4 回まで又は許容できない毒性出現まで、いずれか早い時点まで
	成人及び 12 歳以上の小児で体重 40 kg 以上： 240 mg を 2 週間間隔	4 回の併用療法完了後は、病勢進行又は許容できない毒性出現まで OPDIVO の単剤療法

		又は 480 mg を 4 週間間隔	を継続
		12 歳以上の小児で 体重 40 kg 未満： 3 mg/kg を 2 週間間隔 又は 6 mg/kg を 4 週間間隔	
	切除可能な非小細胞肺がんに対する術前補助療法	360 mg を 3 週間間隔及びプラチナダブレット化学療法を同日に 3 週間間隔	プラチナダブレット化学療法との併用を 3 サイクル
	切除可能な非小細胞肺がんに対する術前及び術後補助療法	術前補助療法：360 mg を 3 週間間隔及びプラチナダブレット化学療法を同日に 3 週間間隔 術後補助療法：480 mg を 4 週間間隔	術前補助療法での化学療法との併用は 4 サイクルまで又は病勢進行又は許容できない毒性出現まで、それに続く術後の OPDIVO の単剤療法による術後補助療法を 13 サイクルまで（約 1 年）又は疾患の再発又は許容できない毒性出現まで
	PD-L1 の発現が認められる転移性非小細胞肺がん	360 mg を 3 週間間隔 イピリムマブ 1 mg/kg を 6 週間間隔	イピリムマブとの併用は病勢進行、許容できない毒性出現又は病勢進行が認められない患者では最大 2 年まで
	転移性又は再発性非小細胞肺がん	360 mg を 3 週間間隔 イピリムマブ 1 mg/kg を 6 週間間隔 及び組織評価に基づいてプラチナダブレット化学療法を 3 週間間隔	イピリムマブとの併用は病勢進行、許容できない毒性出現又は病勢進行が認められない患者では最大 2 年まで
			組織評価に基づいたプラチナダブレット化学療法は 2 サイクル
	悪性胸膜中皮腫	360 mg を 3 週間間隔 イピリムマブ 1 mg/kg を 6 週間間隔	イピリムマブとの併用は病勢進行、許容できない毒性出現又は病勢進行が認められない患者では最大 2 年まで
	進行性腎細胞がん	3 mg/kg を 3 週間間隔 イピリムマブ 1 mg/kg	イピリムマブとの併用は 4 回
		240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔	イピリムマブとの 4 回の併用療法完了後は、病勢進行又は許容できない毒性出現まで OPDIVO の単剤療法を継続
		240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔 OPDIVO はカボザンチニブの 1 日 1 回 40 mg 絶食下単回経口投与と併用する。	OPDIVO：病勢進行、許容できない毒性出現又は最大 2 年間まで
			カボザンチニブ：病勢進行又は許容できない毒性出現まで
	切除不能又は転移性尿路上皮がんの一次治療	360 mg を 3 週間間隔 OPDIVO はシスプラチン及びゲムシタビンとの併用で 3 週間間隔で同日に投与する。	シスプラチン及びゲムシタビンとの併用を最大 6 サイクル
		240 mg を 2 週間間隔 又は 480 mg を 4 週間間隔	最大 6 サイクルの併用療法完了後は、病勢進行、許容できない毒性出現又は初回投与から最大 2 年まで OPDIVO の単剤療法を継続
	高頻度マイクロサテライト不安定性（MSI-H）又はミスマッチ修復機構欠損（dMMR）を有する転移性結腸・直腸がん	成人及び 12 歳以上の小児で 体重 40 kg 以上： 240 mg を 3 週間間隔 イピリムマブ 1 mg/kg	イピリムマブとの併用は最大 4 回
		12 歳以上の小児で 体重 40 kg 未満： 3 mg/kg を 3 週間間隔	

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<tr><td></td><td>イピリムマブ 1 mg/kg</td><td></td></tr>
<tr><td rowspan="2"></td><td>成人及び 12 歳以上の小児で
体重 40 kg 以上：
240 mg を 2 週間間隔
又は
480 mg を 4 週間間隔</td><td rowspan="2">最大 4 回の併用療法完了後は、病勢進行、許容できない毒性出現又は最大 2 年まで OPDIVO の単剤療法を継続</td></tr>
<tr><td>12 歳以上の小児で
体重 40 kg 未満：
3 mg/kg を 2 週間間隔又は
6 mg/kg を 4 週間間隔</td></tr>
<tr><td rowspan="2">肝細胞がん</td><td>1 mg/kg を 3 週間間隔
イピリムマブ 3 mg/kg</td><td>イピリムマブとの併用は最大 4 回</td></tr>
<tr><td>240 mg を 2 週間間隔
又は
480 mg を 4 週間間隔</td><td>最大 4 回の併用療法完了後は、病勢進行、許容できない毒性出現又は最大 2 年まで OPDIVO の単剤療法を継続</td></tr>
<tr><td rowspan="3">食道扁平上皮がん</td><td rowspan="2">240 mg を 2 週間間隔
又は
480 mg を 4 週間間隔
OPDIVO をフルオロピリミジン及びプラチナ製剤を含む化学療法と併用して投与する。</td><td>OPDIVO：病勢進行、許容できない毒性出現又は最大 2 年間まで</td></tr>
<tr><td>化学療法：病勢進行、許容できない毒性出現まで</td></tr>
<tr><td>3 mg/kg を 2 週間間隔
又は
360 mg を 3 週間間隔
及びイピリムマブ 1 mg/kg を 6 週間間隔</td><td>イピリムマブとの併用は病勢進行、許容できない毒性出現又は最大 2 年まで</td></tr>
<tr><td>胃がん、食道胃接合部がん及び食道腺がん</td><td>240 mg を 2 週間間隔
及びフルオロピリミジン及びプラチナ製剤を含む化学療法を 2 週間間隔
又は
360 mg を 3 週間間隔
及びフルオロピリミジン及びプラチナ製剤を含む化学療法を 3 週間間隔</td><td>病勢進行又は許容できない毒性出現まで、あるいは最長 2 年間の投与</td></tr>
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<tr><td>禁忌</td><td>なし</td></tr>
<tr><td>警告及び使用上の注意</td><td>
5.1 重度で致命的な免疫介在性の副作用
OPDIVO は、プログラム細胞死受容体 1（PD-1）又は PD リガンド 1（PD-L1）のいずれかに結合するモノクローナル抗体であり、PD-1/PD-L1 経路を阻害することにより、免疫応答の阻害を解除し、末梢性免疫耐性を破綻させ、免疫介在性の副作用を引き起こす可能性がある。本項に記載の重要な免疫介在性の副作用が、起こりうる重度で致命的な免疫介在性反応のすべてとは言えない。
重度又は致命的な免疫介在性の副作用は、どの器官系又は組織にも起こりうる。PD-1/PD-L1 阻害抗体による治療開始後は、免疫介在性の副作用がいつでも発現する可能性がある。免疫介在性の副作用は通常、PD-1/PD-L1 阻害抗体による治療中に発現するが、PD-1/PD-L1 阻害抗体の中止後に発現することもある。
PD-1/PD-L1 阻害抗体を安全に使用するためには、免疫介在性の副作用を早期に特定し管理することが不可欠である。潜在的な免疫介在性の副作用の臨床症状及び徴候について、患者を注意深くモニタリングする。ベースライン時及び投与期間中は定期的に肝酵素、クレアチニン及び甲状腺機能を評価する。免疫介在性の副作用が疑われる場合、感染を含む他の病因を除外するために適切な精密検査を開始する。必要に応じて専門家へのコンサルテーションを含む医学的管理を速やかに行う。
重症度に応じて OPDIVO の投与を永続的に中断又は中止すること［用法・用量（2.3）参照］。通常、OPDIVO の休薬又は投与中止が必要な場合には、全身性ステロイド薬（1～2 mg/kg/日のプレドニゾン又は同等のステロイドを投与する）を Grade 1 以下に改善するまで投与する。Grade 1 以下に改善した場合、副腎皮質ステロイドの漸減を開始し、少なくとも 1 カ月かけて漸減を継続する。免疫介在性の副作用が副腎皮質ステロイド療法でコントロールできない患者では、他の全身性の免疫抑制剤の投与を考慮する。
全身性のステロイドの投与を必ずしも必要としない副作用（例：内分泌障害及び皮膚反応）に対する毒性管理ガイドラインを以下に記載する。

免疫介在性肺臓炎
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	OPDIVO 投与により免疫介在性肺臓炎（副腎皮質ステロイドの使用を必要とし、他に明確な病因がないものと定義）が発現することがある。他の PD-1/PD-L1 阻害抗体の投与を受けた患者では、過去に胸部放射線療法を受けたことがある患者で肺臓炎の発現率が高い。 *OPDIVO 単剤療法* OPDIVO 単剤療法を受けた患者の 3.1%（61/1994 例）に免疫介在性肺臓炎が発現し、このうち Grade 4（0.1%未満）、Grade 3（0.9%）及び Grade 2（2.1%）の副作用が認められた。免疫介在性肺臓炎のため、1.1%で OPDIVO の投与が永続的に中止され、0.8%で投与が中断された。 肺臓炎を発現した患者の 100%（61/61 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。肺臓炎は 61 例のうち 84%で回復した。肺臓炎により OPDIVO の投与を中断した 15 例のうち、14 例が症状改善後に OPDIVO の投与を再開した。このうち 4 例（29%）に肺臓炎が再発した。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg の併用療法：*OPDIVO 3 mg/kg を 2 週間間隔及びイピリムマブ 1 mg/kg を 6 週間間隔で併用投与された NSCLC 患者では、免疫介在性肺臓炎が 9%（50/576 例）で認められ、うち Grade 4、Grade 3 及び Grade 2 の免疫介在性肺臓炎はそれぞれ 0.5%、3.5%及び 4%に認められた。4 例（0.7%）は肺臓炎により死亡した。免疫介在性肺臓炎により、5%の患者で OPDIVO とイピリムマブの併用投与が永続的に中止され、3.6%で投与が中断された。 肺臓炎が発現した患者の全例で全身性の副腎皮質ステロイドによる治療が必要とされた。肺臓炎は 72%の患者で回復した。また、約 13%の患者（2/16 例）で OPDIVO とイピリムマブの併用療法再開後に肺臓炎の再発が認められた。 <u>免疫介在性大腸炎</u> OPDIVO 投与により免疫介在性大腸炎（副腎皮質ステロイドの使用を必要とし、他に明確な病因がないものと定義）が発現することがある。大腸炎の定義に含まれる一般的な症状は下痢であった。副腎皮質ステロイド抵抗性免疫介在性大腸炎が発現した患者にサイトメガロ・ウイルス感染／再熱が報告された。副腎皮質ステロイド抵抗性大腸炎が発現した場合は、別の原因を排除するために感染の精密検査の再実施を考慮する必要がある。 *OPDIVO 単剤療法* OPDIVO の単剤投与を受けた患者の 2.9%（58/1994 例）に免疫介在性大腸炎が発現し、このうち Grade 3（1.7%）及び Grade 2（1%）の副作用が認められた。免疫介在性大腸炎のため、患者の 0.7%で OPDIVO の投与が永続的に中止され、0.9%で投与が中断された。 大腸炎患者の 100%（58/58 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。4 例の患者で高用量の副腎皮質ステロイドに加えインフリキシマブの投与が必要とされた。大腸炎は 58 例のうち 86%で回復した。大腸炎のため OPDIVO を中断した 18 例のうち、16 例で症状改善後に OPDIVO の投与を再開した。このうち 12 例（75%）で大腸炎の再発が認められた。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg の併用療法*：免疫介在性大腸炎は、OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg を 3 週間間隔で併用投与した悪性黒色腫患者又は HCC 患者の 25%（115/456 例）に発現し、このうち Grade 4（0.4%）、Grade 3（14%）、Grade 2（8%）の副作用が認められた。免疫介在性大腸炎のため、14%の患者で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、4.4%で投与が中断された。 大腸炎患者の 100%（115/115 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。約 23%の患者で高用量の副腎皮質ステロイドに加えインフリキシマブの投与を必要とした。大腸炎は 115 例の患者の 93%で回復した。大腸炎のため OPDIVO とイピリムマブの併用投与を中断した 20 例のうち、16 例で症状改善後に投与を再開した。このうち 9 例（56%）で大腸炎の再発が認められた。 *OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg の併用療法*：免疫介在性大腸炎は、OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg を 3 週間間隔で併用投与した RCC 又は CRC の 9%（60/666 例）に認められ、このうち Grade 3（4.4%）及び Grade 2（3.7%）の副作用が認められた。免疫介在性大腸炎のため、RCC 又は CRC の患者の 3.2%で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、2.7%で投与が中断された。 大腸炎患者の 100%（60/60 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。約 23%の患者で高用量の副腎皮質ステロイドに加えインフリキシマブの投与を必要とした。大腸炎は 60 例のうち 95%で回復した。大腸炎のため OPDIVO とイピリムマブの併用投与を中断した 18 例のうち、16 例で症状改善後に投与を再開した。このうち 10 例（63%）で大腸炎の再発が認められた。 <u>免疫介在性肝炎及び肝毒性</u> OPDIVO 投与により免疫介在性肝炎（副腎皮質ステロイドの使用を必要とし、他に明確な病因がないものと定義）が発現することがある。 *OPDIVO 単剤療法*

	OPDIVO の単剤投与を受けた患者の 1.8%（35/1994 例）に免疫介在性肝炎が発現し、このうち Grade 4（0.2%）、Grade 3（1.3%）、Grade 2（0.4%）の副作用が認められた。免疫介在性肝炎のため、0.7%で OPDIVO の投与が永続的に中止され、0.6%で投与が中断された。 肝炎患者の 100%（35/35 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。2 例の患者は、高用量の副腎皮質ステロイドに加えミコフェノール酸の投与を必要とした。肝炎は 35 例の患者のうち 91%で回復した。肝炎のため OPDIVO を中断した 12 例のうち、11 例で症状改善後に OPDIVO の投与を再開した。このうち 9 例（82%）で肝炎の再発が認められた。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ3 mg/kg の併用療法*：免疫介在性肝炎は、OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg の 3 週間間隔で併用投与を受けた悪性黒色腫患者又は HCC 患者の 15%（70/456 例）に発現し、このうち Grade 4（2.4%）、Grade 3（11%）、Grade 2（1.8%）の副作用が認められた。免疫介在性肝炎のため、患者の 8%で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、3.5%で投与が中断された。 肝炎患者の 100%（70/70 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。患者の約 9%は、高用量の副腎皮質ステロイドに加えミコフェノール酸の投与を必要とした。肝炎は 70 例のうち 91%で回復した。肝炎の発現により OPDIVO 又はイピリムマブの投与が中断された 16 例のうち、14 例で症状改善後に投与を再開した。このうち 8 例（57%）で肝炎の再発が認められた。 *OPDIVO 3 mg/kg とイピリムマブ1 mg/kg の併用療法*：免疫介在性肝炎は、OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg を 3 週間間隔で併用投与した RCC 患者又は CRC 患者の 7%（48/666 例）に発現し、このうち Grade 4（1.2%）、Grade 3（4.9%）及び Grade 2（0.4%）の副作用が認められた。免疫介在性肝炎により、RCC 患者又は CRC 患者の 3.6%で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、2.6%で投与が中断された。 肝炎患者の 100%（48/48 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。患者の約 19%は、高用量の副腎皮質ステロイドに加えミコフェノール酸の投与が必要とされた。肝炎は 48 例のうち 88%で回復した。肝炎の発現により OPDIVO 及びイピリムマブの投与を中断した 17 例のうち、14 例で症状改善後に投与を再開した。このうち 10 例（71%）で肝炎の再発が認められた。 *OPDIVO とカボザンチニブの併用療法* OPDIVO とカボザンチニブの併用により肝毒性が発現する可能性があり、Grade 3 及び 4 の ALT 及び AST 増加の発現頻度は OPDIVO 単剤投与時と比較して高かった。投与開始前及び投与期間中は定期的に肝酵素をモニタリングすること。各薬剤の単剤投与時よりも、肝酵素のより頻繁なモニタリングを考慮する。肝酵素上昇が認められた場合は、OPDIVO 及びカボザンチニブを休薬し、副腎皮質ステロイドの投与を考慮すること*［用法・用量（2.3）参照］*。 OPDIVO とカボザンチニブの併用により、Grade 3 及び 4 の ALT 又は AST の増加が患者の 11%で認められた*［副作用（6.1）参照］*。ALT 又は AST が ULN の 3 倍超（Grade ≥2）が 83 例に認められ、このうち 23 例（28%）は全身性の副腎皮質ステロイドが投与された。ALT 又は AST は 74 例（89%）で Grade 0～1 に回復した。Grade 2 以上の ALT 増加又は AST 増加が認められた 44 例のうち、OPDIVO（11 例）若しくはカボザンチニブ（9 例）のいずれかを単独又は併用（24 例）で投与を再開したとき、Grade 2 以上の ALT 増加又は AST 増加の再発は、OPDIVO 単剤投与で 2 例、カボザンチニブ単剤投与で 2 例、OPDIVO とカボザンチニブの併用投与で 7 例に認められた。 <u>免疫介在性内分泌障害</u> *副腎機能不全* OPDIVO は原発性又は二次性副腎機能不全を引き起こす可能性がある。Grade 2 以上の副腎機能不全に対しては、臨床的に必要であればホルモン補充を含む対症療法を開始する。重症度*［用法・用量（2.3）参照］*に応じて OPDIVO の投与を中断する。 *OPDIVO 単剤療法* OPDIVO の単剤投与を受けた患者の 1%（20/1994 例）に副腎機能不全が発現し、このうち Grade 3（0.4%）及び Grade 2（0.6%）の副作用が認められた。副腎機能不全のため、患者の 0.1%で OPDIVO の投与が永続的に中止され、0.4%で投与が中断された。 副腎機能不全が認められた患者の約 85%にホルモン補充療法を行った。副腎機能不全患者の 90%（18/20 例）で全身性の副腎皮質ステロイドによる治療が必要とされた。副腎機能不全は 20 例の患者のうち 35%で回復した。副腎機能不全のため OPDIVO を中断した 8 例のうち、4 例で症状改善後に OPDIVO の投与を再開し、いずれも副腎機能不全が持続しているためホルモン補充療法を必要とした。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ3 mg/kg の併用療法*：OPDIVO 1 mg/kg 及びイピリムマブ 3 mg/kg を 3 週間間隔で併用投与された悪性黒色腫患者及び HCC 患者で、副腎機能不全が患者の 8%（35/456 例）で発現し、このうち Grade 4（0.2%）、Grade 3（2.4%）及び Grade 2（4.2%）の副作用が認められた。副腎機能不全のため、患者の 0.4%で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、2%で投与が中断された。

	副腎機能不全患者の約 71%（25/35 例）が、副腎皮質ステロイドの全身投与を含むホルモン補充療法を受けた。副腎機能不全は 35 例のうち 37%で回復した。副腎機能不全により OPDIVO 及びイピリムマブの投与を中断した 9 例のうち、7 例で症状改善後に投与を再開し、いずれも副腎機能不全が持続しているためホルモン補充療法を必要とした。 *OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg の併用療法*：OPDIVO 3 mg/kg 及びイピリムマブ 1 mg/kg の 3 週間間隔で併用投与された RCC 又は CRC 患者で、副腎機能不全が 7%（48/666 例）で発現し、このうち Grade 4（0.3%）、Grade 3（2.5%）、Grade 2（4.1%）の副作用が認められた。副腎機能不全のため、RCC 患者又は CRC 患者の 1.2%で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、2.1%で投与が中断された。 副腎機能不全患者の約 94%（45/48 例）が、副腎皮質ステロイドの全身投与を含むホルモン補充療法を受けた。副腎機能不全は 48 例の患者のうち 29%で回復した。副腎機能不全のため OPDIVO 及びイピリムマブの投与を中断した 14 例のうち、11 例で症状改善後に投与を再開した。いずれもホルモン補充療法を受け、2 例（18%）に副腎機能不全の再発が認められた。 *OPDIVO とカボザンチニブの併用療法* OPDIVO とカボザンチニブを併用投与された RCC 患者で、副腎機能不全が 4.7%（15/320 例）に発現し、このうち Grade 3（2.2%）及び Grade 2（1.9%）の副作用が認められた。副腎機能不全のため、RCC 患者の 0.9%で OPDIVO 及びカボザンチニブの投与が永続的に中止され、2.8%で投与が中断された。 副腎機能不全患者の約 80%（12/15 例）が、副腎皮質ステロイドの全身投与を含むホルモン補充療法を受けた。副腎機能不全は患者 15 例の 27%（4 例）で回復した。OPDIVO 及びイピリムマブの投与を中断した 9 例のうち、6 例で症状改善後に投与を再開した。いずれもホルモン補充療法を受け、2 例に副腎機能不全の再発が認められた。 *下垂体炎* OPDIVO は免疫介在性下垂体炎を引き起こす可能性がある。下垂体炎は、頭痛、羞明、視野欠損などの腫瘤効果に関連する急性症状を呈することがある。下垂体炎は下垂体機能低下症を引き起こしうる。臨床的に必要な場合、ホルモン補充療法を開始する。重症度に応じて OPDIVO の投与を永続的に中断又は中止すること*［用法・用量（2.3）参照］*。 *OPDIVO 単剤療法* OPDIVO の単剤投与を受けた患者の 0.6%（12/1994 例）に下垂体炎が発現し、このうち Grade 3（0.2%）及び Grade 2（0.3%）の副作用が認められた。下垂体炎のため、永続的に OPDIVO の投与中止に至った患者は 0.1%未満であり、0.2%で投与が中断された。 下垂体炎患者の約 67%（8/12 例）が副腎皮質ステロイドの全身投与などのホルモン補充療法を受けている。下垂体炎は 12 例の患者のうち 42%で回復した。下垂体炎のため OPDIVO の投与を中断した 3 例の患者のうち、2 例で症状改善後に OPDIVO の投与を再開し、下垂体炎の再発は認められなかった。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg の併用療法*：OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg を 3 週間間隔で投与された悪性黒色腫又は HCC 患者で、下垂体炎が 9%（42/456 例）に発現し、このうち Grade 3（2.4%）と Grade 2（6%）の副作用が認められた。下垂体炎のため、患者の 0.9%で OPDIVO 及びイピリムマブ併用投与が永続的に中止され、4.2%で投与が中断された。 下垂体炎患者の約 86%がホルモン補充療法を受けた。全身性の副腎皮質ステロイドは下垂体炎患者の 88%（37/42 例）で必要であった。下垂体炎は 42 例の患者のうち 38%で回復した。下垂体炎のため OPDIVO 及びイピリムマブの投与を中断した 19 例のうち、9 例で症状改善後に投与を再開した。このうち 1 例（11%）に下垂体炎の再発が認められた。 *OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg の併用療法*：OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg を 3 週間間隔で投与された RCC 患者又は CRC 患者で、下垂体炎は 4.4%（29/666 例）に発現し、このうち Grade 4（0.3%）、Grade 3（2.4%）、Grade 2（0.9%）の副作用が認められた。下垂体炎のため、患者の 1.2%で OPDIVO 及びイピリムマブの併用投与が永続的に中止され、2.1%で投与を中断した。 下垂体炎患者の約 72%（21/29 例）が全身性の副腎皮質ステロイドなどのホルモン補充療法を受けていた。下垂体炎は 29 例のうち 59%で回復した。下垂体炎のため OPDIVO 及びイピリムマブの投与を中断した 14 例のうち、11 例で症状改善後に投与を再開した。このうち 2 例（18%）で下垂体炎の再発が認められた。 *甲状腺障害* OPDIVO 投与により免疫介在性甲状腺障害が発現することがある。甲状腺炎は内分泌障害の有無に関わらず発現する。甲状腺機能低下症は甲状腺機能亢進症に続発することがある。臨床的に必要な場合、ホルモン補充療法又は医学的管理を開始する。重症度に応じて OPDIVO の投与を永続的に中断又は中止すること*［用法・用量（2.3）参照］*。 *甲状腺炎*

	OPDIVO 単剤療法 OPDIVO の単剤投与を受けた患者の 0.6%（12/1994 例）に甲状腺炎が発現し、このうち Grade 2（0.2%）の副作用が認められた。甲状腺炎により OPDIVO の永続的な投与中止に至った患者は認められず、0.2%で OPDIVO の投与が中断された。 全身性の副腎皮質ステロイドは甲状腺炎患者の 17%（2/12 例）で必要であった。甲状腺炎は 12 例のうち 58%で回復した。甲状腺炎のため OPDIVO の投与を中断した 3 例のうち、1 例が症状改善後に OPDIVO の投与を再開し、甲状腺炎の再発は認められなかった。 *甲状腺機能亢進症* *OPDIVO 単剤療法* OPDIVO の単剤投与を受けた患者の 2.7%（54/1994 例）に甲状腺機能亢進症が発現し、このうち Grade 3（0.1%未満）及び Grade 2（1.2%）の副作用が認められた。甲状腺機能亢進症により OPDIVO の永続的な投与中止に至った患者は認められず、0.4%で投与が中断された。 甲状腺機能亢進症患者の約 19%がメチマゾール、7%がカルビマゾール、4%がプロピルチオウラシルの投与を受けた。全身性の副腎皮質ステロイドは患者の 9%（5/54 例）で必要であった。甲状腺機能亢進症は 54 例のうち 76%で回復した。甲状腺機能亢進症のため OPDIVO の投与を中断した 7 例のうち、4 例が症状改善後に OPDIVO の投与を再開し、甲状腺機能亢進症の再発は認められなかった。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ3 mg/kg の併用療法*：OPDIVO 1 mg/kg 及びイピリムマブ 3 mg/kg を 3 週間間隔で併用投与された悪性黒色腫患者又は HCC 患者で、甲状腺機能亢進症が患者の 9%（42/456 例）に発現し、このうち Grade 3（0.9%）及び Grade 2（4.2%）の副作用が認められた。甲状腺機能亢進症のため OPDIVO 及びイピリムマブ併用投与が永続的に中止された患者は認められず、2.4%で投与が中断された。 甲状腺機能亢進症患者の約 26%がメチマゾールの投与を受け、21%がカルビマゾールの投与を受けた。患者の 17%（7/42 例）が副腎皮質ステロイドの全身投与を必要とした。甲状腺機能亢進症は 42 例のうち 91%で回復した。甲状腺機能亢進症のため OPDIVO 及びイピリムマブの併用投与を中断した 11 例のうち、8 例で症状改善後に投与を再開した。このうち 1 例（13%）は甲状腺機能亢進症の再発が認められた。 *OPDIVO 3 mg/kg 及びイピリムマブ1 mg/kg 併用療法*：OPDIVO 3 mg/kg 及びイピリムマブ 1 mg/kg を 3 週間間隔で併用投与した RCC 患者又は CRC 患者の 12%（80/666 例）に甲状腺機能亢進症が発現し、Grade 3（0.6%）、Grade 2（4.5%）の副作用が認められた。甲状腺機能亢進症のため OPDIVO 及びイピリムマブ併用投与が永続的に中止された患者は認められず、2.3%で投与が中断された。 甲状腺機能亢進症を発現した RCC 患者又は CRC 患者 80 例のうち、約 16%がメチマゾールの投与を受け、3%がカルビマゾールの投与を受けた。全身性の副腎皮質ステロイドは甲状腺機能亢進症患者の 20%（16/80 例）で必要であった。甲状腺機能亢進症は 80 例のうち 85%で回復した。甲状腺機能亢進症のため OPDIVO 及びイピリムマブの併用投与を中断した 15 例のうち、11 例で症状改善後に投与を再開した。このうち 3 例（27%）で甲状腺機能亢進症の再発が認められた。 *甲状腺機能低下症* *OPDIVO 単剤療法* OPDIVO の単剤投与を受けた患者の 8%（163/1994 例）に甲状腺機能低下症が発現し、このうち Grade 3（0.2%）及び Grade 2（4.8%）の副作用が認められた。甲状腺機能低下症により OPDIVO の投与を永続的に中止した患者は認められず、0.5%で投与が中断された。 甲状腺機能低下症患者の約 79%がレボチロキシンの投与を受けた。全身性の副腎皮質ステロイドは甲状腺機能低下症患者の 3.1%（5/163 例）で必要であった。甲状腺機能低下症は 163 例の患者のうち 35%で回復した。甲状腺機能低下症のため OPDIVO を中断した 9 例のうち、3 例は症状改善後に OPDIVO の投与を再開した。このうち 1 例（33%）で甲状腺機能低下症の再発が認められた。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ3 mg/kg の併用療法*：OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg を 3 週間間隔で併用投与された悪性黒色腫患者又は HCC 患者の 20%（91/456 例）に甲状腺機能低下症が発現し、このうち Grade 3（0.4%）と Grade 2（11%）の副作用が認められた。甲状腺機能低下症のため、患者の 0.9%で OPDIVO 及びイピリムマブの併用投与が永続的に中止され、0.9%で投与が中断された。 甲状腺機能低下症患者の約 89%がレボチロキシンの投与を受けた。全身性の副腎皮質ステロイドは甲状腺機能低下症患者の 2.2%（2/91 例）で必要であった。甲状腺機能低下症は 91 例の患者のうち 41%で回復した。甲状腺機能低下症のため OPDIVO 及びイピリムマブの併用投与を中断した 4 例のうち、2 例で症状改善後に投与を再開し、甲状腺機能低下症の再発は認められなかった。 *OPDIVO 3 mg/kg とイピリムマブ1 mg/kg の併用療法*：OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg を 3 週間間隔で併用投与された RCC 患者又は CRC 患者の 18%（122/666 例）に甲状腺機能低下症が発現し、このうち Grade 3（0.6%）と Grade 2（11%）の副作用が認められた。甲状腺機能低下症のため、

	RCC 患者又は CRC 患者の 0.2%で OPDIVO 及びイピリムマブの併用投与が永続的に中止され、1.4%で投与が中断された。 甲状腺機能低下症が発現した RCC 患者又は CRC 患者 122 例のうち、約 82%がレボチロキシンの投与を受けた。全身性の副腎皮質ステロイドは甲状腺機能低下症患者の 7%（9/122 例）で必要であった。甲状腺機能低下症は、122 例のうち 27%で回復した。甲状腺機能低下症のため OPDIVO 及びイピリムマブの併用投与を休薬した 9 例のうち、5 例で症状改善後に投与が再開された。このうち 1 例（20%）で甲状腺機能低下症の再発が認められた。 *1 型糖尿病（糖尿病性ケトアシドーシスを伴うことがある）* 高血糖又はその他の糖尿病の徴候及び症状について患者をモニタリングする。臨床的に必要な場合、インスリンによる治療を開始する。重症度に応じて OPDIVO の投与を中断すること*［用法・用量（2.3）参照］*。 *OPDIVO 単剤療法* OPDIVO を投与された患者の 0.9%（17/1994 例）に糖尿病が発現し、このうち Grade 3（0.4%）及び Grade 2（0.3%）の副作用が認められた。また、2 例に糖尿病性ケトアシドーシスが認められた。糖尿病のため OPDIVO の永続的な投与中止に至った患者は認められず、0.1%で投与が中断された。 いずれの糖尿病患者も全身性の副腎皮質ステロイドを必要としなかった。糖尿病は 17 例の患者のうち 29%で回復した。糖尿病のため OPDIVO を休薬した 2 例は、いずれも症状改善後に OPDIVO の投与を再開し、糖尿病の再発は認められなかった。 腎機能障害を伴う免疫介在性腎炎 OPDIVO は免疫介在性腎炎（ステロイドの使用を必要とし、他に明確な病因がないことと定義）が発現することがある。 *OPDIVO 単剤療法* OPDIVO の単剤投与を受けた患者の 1.2%（23/1994 例）に免疫介在性腎炎及び腎機能障害が発現し、このうち Grade 4（0.1%未満）、Grade 3（0.5%）及び Grade 2（0.6%）の副作用が認められた。免疫介在性腎炎及び腎機能障害により、0.3%の患者で OPDIVO の投与が永続的に中止され、0.4%で投与が中断された。 腎炎と腎機能障害患者の 100%（23/23 例）で全身性の副腎皮質ステロイドが必要であった。腎炎及び腎機能障害は 23 例のうち 78%で回復した。腎炎又は腎機能障害のため OPDIVO の投与を中断した 7 例のうち、いずれも症状改善後に OPDIVO の投与を再開した。このうち 1 例（14%）に腎炎又は腎機能障害の再発が認められた。 免疫介在性の皮膚の副作用 OPDIVO 投与により、免疫介在性発疹や皮膚炎（ステロイドの使用を必要とし、他に明確な病因はないことと定義）が発現することがある。スティーブンス・ジョンソン症候群、中毒性表皮壊死症（TEN）及び DRESS（好酸球増加と全身症状を伴う薬物性発疹）を含む剥脱性皮膚炎が PD-1/PD-L1 阻害抗体により発現している。軽度から中等度の非剥脱性発疹の治療には、皮膚軟化剤の外用及び/又は副腎皮質ステロイドの外用で十分なことがある。重症度に応じて OPDIVO の投与を永続的に中断又は中止すること*［用法・用量（2.3）参照］*。 *OPDIVO 単剤療法* 患者の 9%（171/1994 例）に免疫介在性発疹が発現し、このうち Grade 3（1.1%）及び Grade 2（2.2%）の副作用が認められた。免疫介在性発疹のため、0.3%の患者で OPDIVO の投与が永続的に中止され、0.5%で投与が中断された。 免疫介在性発疹患者の 100%（171/171 例）で全身性の副腎皮質ステロイドが必要であった。発疹は 171 例のうち 72%で回復した。免疫介在性発疹のため OPDIVO の投与を中断した 10 例のうち、9 例で症状改善後に OPDIVO の投与を再開した。このうち 3 例（33%）で免疫介在性発疹の再発が認められた。 *OPDIVO とイピリムマブの併用療法* *OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg の併用療法*：OPDIVO 1 mg/kg とイピリムマブ 3 mg/kg を 3 週間間隔で併用投与された悪性黒色腫患者又は HCC 患者の 28%（127/456 例）に免疫介在性発疹が発現し、このうち Grade 3（4.8%）及び Grade 2（10%）の副作用が認められた。免疫介在性発疹により、0.4%の患者で OPDIVO 及びイピリムマブの併用投与が永続的に中止され、3.9%で投与が中断された。 免疫介在性発疹患者の 100%（127/127 例）で全身性の副腎皮質ステロイドが必要であった。発疹は 127 例のうち 84%で回復した。免疫介在性発疹のため OPDIVO 及びイピリムマブの併用投与を中断した 18 例のうち、15 例で症状改善後に投与を再開した。このうち 8 例（53%）で免疫介在性発疹の再発が認められた。 *OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg の併用療法*：OPDIVO 3 mg/kg とイピリムマブ 1 mg/kg を 3 週間間隔で併用投与された RCC 患者又は CRC 患者の 16%（108/666 例）に免疫介在性発疹が発現し、このうち Grade 3（3.5%）、Grade 2（4.2%）の副作用が認められた。免疫介在性発疹のため、

	RCC 患者又は CRC 患者の 0.5%で OPDIVO 及びイピリムマブの併用投与が永続的に中止され、2.0%で投与が中断された。 免疫介在性発疹患者の 100%（108/108 例）で全身性の副腎皮質ステロイドが必要であった。発疹は 108 例のうち 75%で回復した。免疫介在性発疹のため OPDIVO 及びイピリムマブの併用投与を中断した 13 例のうち、11 例で症状改善後に投与を再開した。このうち 5 例（46%）で免疫介在性発疹の再発が認められた。 その他の免疫介在性の副作用 以下の臨床的に重要な免疫介在性の有害事象は、OPDIVO 又は OPDIVO とイピリムマブの併用投与を受けた患者の（特記しない限り）1%未満で発現した事象か、他の PD-1/PD-L1 阻害抗体により報告されたものである。これらの副作用の一部では重度又は死亡例が報告されている。 *心臓障害／血管障害*：心筋炎、心膜炎、血管炎 *神経系障害*：髄膜炎、脳炎、脊髄炎・脱髄、筋無力症候群・重症筋無力症（増悪を含む）、ギラン・バレー症候群、神経不全麻痺、自己免疫性ニューロパチー *眼障害*：ぶどう膜炎、虹彩炎、及びその他の眼炎症性毒性が生じることがある。網膜剥離を伴う症例もある。失明を含む様々な程度の視力障害が起こりうる。ぶどう膜炎が他の免疫介在性の副作用と併発した場合、フォークト・小柳・原田病は、永久的な視力喪失のリスクを低下させるために全身ステロイドによる治療が必要な可能性があるため、この症候群を検討する。 *胃腸障害*：血清アミラーゼ及びリパーゼ増加を含む膵炎、胃炎、十二指腸炎 *筋骨格系及び結合組織障害*：筋炎／多発性筋炎、横紋筋融解症及び関連する後遺症（腎不全、関節炎、多発性筋痛症を含む） *内分泌障害*：副甲状腺機能低下症 *その他（血液学的障害／免疫障害）*：溶血性貧血、再生不良性貧血、血球貪食性リンパ組織球症、全身性炎症反応症候群、組織球性壊死性リンパ節炎（菊池リンパ節炎）、サルコイドーシス、免疫性血小板減少性紫斑病、固形臓器移植拒絶反応、その他の移植（角膜移植を含む）拒絶反応 **5.2 注入に伴う反応** OPDIVO 投与により、重度の注入に伴う反応が発現することがあり、臨床試験では、患者の 1%未満で報告された。重度又は生命を脅かす注入に伴う反応が患者に認められた場合は、OPDIVO の投与を中止する。軽度又は中等度の注入に伴う反応が患者に認められた場合は、投与を中断するか、注入速度を下げる*［用法・用量（2.3）参照］*。 OPDIVO 単剤療法 OPDIVO を単剤で 60 分かけて点滴静注された患者の 6.4%（127/1994 例）で注入に伴う反応が認められた。 より速い注入速度で投与した場合の薬物動態及び安全性を評価した試験では、OPDIVO を 60 分かけて点滴静注された患者の 2.2%（8/368 例）、30 分かけて点滴静注された患者の 2.7%（10/369 例）で注入に伴う反応が認められた。また、それぞれの患者の 0.5%（2/368 例）及び 1.4%（5/369 例）で、投与 48 時間以内に発現した副作用により OPDIVO の投与延期、永続的な投与中止又は投与中断に至った。 OPDIVO とイピリムマブの併用療法 *OPDIVO 1 mg/kg とイピリムマブ3 mg/kg の併用療法* OPDIVO 1 mg/kg 及びイピリムマブ 3 mg/kg を 3 週間間隔で併用投与された悪性黒色腫患者及び HCC 患者のそれぞれ 2.5%（10/407 例）及び 8%（4/49 例）に注入に伴う反応が認められた。 *OPDIVO 3 mg/kg とイピリムマブ1 mg/kg の併用療法* OPDIVO 3 mg/kg 及びイピリムマブ 1 mg/kg を 3 週間間隔で併用投与された RCC 患者の 5.1%（28/547 例）及び CRC 患者の 4.2%（5/119 例）で注入に伴う反応が認められた。OPDIVO 3 mg/kg を 2 週間間隔で投与し、イピリムマブ 1 mg/kg を 6 週間間隔で併用投与された悪性胸膜中皮腫患者の 12%（37/300 例）で注入に伴う反応が認められた。 **5.3 同種造血幹細胞移植の合併症** PD-1 受容体阻害抗体の投与前後に同種造血幹細胞移植（HSCT）を受ける患者では、致命的な事象を含む重篤な合併症が発現する場合がある。移植関連の合併症には、超急性移植片対宿主病（GVHD）、急性 GVHD、慢性 GVHD、毒性軽減前処置後の肝中心静脈閉塞症（VOD）及びステロイドの投与を必要とする発熱性症候群（感染原因が特定されていない）などが挙げられる*[副作用（6.1）参照]*。これらの合併症は、PD-1 阻害と同種 HSCT の間に治療を介入させても生じる可能性がある。 移植関連の合併症の徴候について患者をよく観察し、直ちに処置すること。同種 HSCT 施行の前、又は後には PD-1 受容体阻害抗体による治療のベネフィットとリスクを考慮すること。 **5.4 胚・胎児毒性**

	作用機序及び動物試験のデータから、OPDIVO は妊娠中の女性に投与すると胎児に悪影響を及ぼすおそれがある。動物を用いた生殖試験では、ニボルマブをカニクイザルに器官形成期の開始から分娩まで投与すると、流産及び未熟児死亡が増加した。妊娠中の女性には、胎児へのリスクを説明すること。妊娠する可能性のある女性には、OPDIVO の投与期間中及び最終投与後 5 カ月間は、効果的な避妊法を用いるように指導する*［特定の集団における使用（8.1、8.3）参照］*。 **5.5 多発性骨髄腫患者においてサリドマイド類似薬及びデキサメタゾンに OPDIVO を追加投与した際の死亡率の増加** 多発性骨髄腫を対象とした無作為化試験において、これまでに PD-1 又は PD-L1 阻害抗体を投与されたことのない患者にサリドマイド類似薬及びデキサメタゾンに加えて OPDIVO を含む PD-1 阻害抗体を追加することで死亡率が増加した。多発性骨髄腫患者の治療として、サリドマイド類似薬及びデキサメタゾンに PD-1 又は PD-L1 阻害抗体を加えた併用療法は管理された臨床試験を除いて推奨されない。
添付文書の改訂日	2025 年 5 月

表 1.6.1-3　欧州添付文書の概要

国名	EU
販売名	OPDIVO 10 mg/mL concentrate for solution for infusion
会社名	Bristol-Myers Squibb Pharma EEIG, Uxbridge Business Park, Sanderson Road Uxbridge UB8 1DH, United Kingdom
一般的名称	ニボルマブ
承認年月日	2015 年 6 月 19 日
剤形・含量	点滴溶液用濃縮液（滅菌濃縮液） 濃縮液 1 mL 中にニボルマブ 10 mg を含有する。 4 mL 充填バイアル中にニボルマブ 40 mg を含有する。 10 mL 充填バイアル中にニボルマブ 100 mg を含有する。 12 mL 充填バイアル中にニボルマブ 120 mg を含有する。 24 mL 充填バイアル中にニボルマブ 240 mg を含有する。 ニボルマブは遺伝子組換え技術により、チャイニーズハムスター卵巣細胞を用いて製造される。
効能・効果	悪性黒色腫 OPDIVOは、単剤療法又はイピリムマブとの併用療法として、成人及び12歳以上の青年の進行（切除不能又は転移性）悪性黒色腫患者の治療を適応とする。 ニボルマブ単剤療法と比較して、ニボルマブ及びイピリムマブの併用療法の無増悪生存期間（PFS）及び全生存期間（OS）の延長は、PD-L1発現率の低い患者のみで確立されている（4.4項及び5.1項参照）。 悪性黒色腫に対する術後補助療法 OPDIVOは、単剤療法として、IIB期又はIIC期の悪性黒色腫又はリンパ節転移若しくは転移を伴う悪性黒色腫で完全切除を受けた成人及び12歳以上の青年の患者の術後補助療法の治療を適応とする（5.1項参照）。 非小細胞肺がん（NSCLC） OPDIVOは、イピリムマブ及びプラチナダブレット化学療法2サイクルとの併用療法として、EGFR又はALK遺伝子変異陰性の成人の転移性非小細胞肺がん患者の一次治療を適応とする。 OPDIVOは、単剤療法として、化学療法による前治療後に局所進行又は転移した成人の非小細胞肺がん患者の治療を適応とする。 NSCLCに対する術前補助療法 OPDIVOは、プラチナ製剤を含む化学療法との併用療法として、PD-L1発現率が1%以上で再発リスクが高い切除可能な非小細胞肺がんの成人患者の術前補助療法の治療を適応とする（患者を選択する基準については、5.1項参照）。 NSCLCに対する術前及び術後補助療法 OPDIVOは、術前補助療法としてプラチナ製剤を含む化学療法と併用した後、術後補助療法としてOPDIVO単剤療法を行う、PD-L1発現率が1%以上で再発リスクが高い切除可能な非小細胞肺がんの成人患者の治療を適応とする（患者を選択する基準については、5.1項参照）。 悪性胸膜中皮腫（MPM） OPDIVOは、イピリムマブとの併用療法として、成人の切除不能な悪性胸膜中皮腫患者の一次治療を適応とする。

	腎細胞がん（RCC） OPDIVOは、単剤療法として、化学療法による前治療後に進行した成人の腎細胞がん患者の治療を適応とする。 OPDIVOは、イピリムマブとの併用療法として、intermediate又はpoorリスクの成人の進行性腎細胞がん患者の一次治療を適応とする（5.1項参照）。 OPDIVOは、カボザンチニブとの併用療法として、成人の進行性腎細胞がん患者の一次治療を適応とする（5.1項参照）。 古典的ホジキンリンパ腫（cHL） OPDIVOは、単剤療法として、自家造血幹細胞移植（ASCT）及びブレンツキシマブ ベドチン治療の後に再発又は治療抵抗性を示した、成人の古典的ホジキンリンパ腫（cHL）患者の治療を適応とする。 頭頸部扁平上皮がん（SCCHN） OPDIVOは、単剤療法として、プラチナ製剤を含む化学療法による治療中又は治療後に再発又は転移した、成人の頭頸部扁平上皮がん患者の治療を適応とする（5.1項参照）。 尿路上皮がん OPDIVOは、シスプラチン及びゲムシタビンとの併用療法として、成人の切除不能又は転移性の尿路上皮がん患者の一次治療を適応とする。 OPDIVOは、単剤療法として、プラチナ製剤を含む化学療法による治療が奏功しなかった、切除不能な局所進行又は転移性の成人の尿路上皮がん患者の治療を適応とする。 尿路上皮がんに対する術後補助療法 OPDIVOは、単剤療法として、根治切除後に再発リスクの高いPD-L1発現率が1%以上の筋層浸潤性尿路上皮がん（MIUC）の成人患者の術後補助療法の治療を適応とする（5.1項参照）。 ミスマッチ修復機構欠損（dMMR）又は高頻度マイクロサテライト不安定性（MSI-H）を有する結腸・直腸がん（CRC） OPDIVOは、イピリムマブとの併用療法として、以下の状況におけるミスマッチ修復機構欠損又は高頻度マイクロサテライト不安定性を有する結腸・直腸がんの成人患者の治療を適応とする。 • 切除不能又は転移性の結腸・直腸がんの一次治療 • フルオロピリミジン製剤を含む併用化学療法による前治療後の転移性結腸・直腸がんの治療（5.1 項参照） 食道扁平上皮がん（OSCC） OPDIVOは、イピリムマブとの併用療法として、PD-L1発現率が1%以上の切除不能な進行、再発又は転移性の食道扁平上皮がんの成人患者の一次治療を適応とする。 OPDIVOは、フルオロピリミジン及びプラチナ製剤を含む化学療法との併用療法として、PD-L1発現率が1%以上の切除不能な進行、再発又は転移性の食道扁平上皮がんの成人患者の一次治療を適応とする。 OPDIVOは、単剤療法として、フルオロピリミジン及びプラチナ製剤を含む化学療法による前治療後の切除不能な進行、再発又は転移性の食道扁平上皮がんの成人患者の治療を適応とする。 食道がん（OC）又は食道胃接合部がん（GEJC）に対する術後補助療法 OPDIVOは、単剤療法として、術前補助化学放射線療法後に病理学的残存病変を有する食道がん又は食道胃接合部がんの成人患者の術後補助療法の治療を適応とする（5.1項参照）。 胃がん、食道胃接合部（GEJ）がん又は食道腺がん OPDIVOは、フルオロピリミジン及びプラチナ製剤を含む化学療法との併用療法として、combined positive score（CPS）が5以上のPD-L1陽性でHER-2陰性の進行又は転移性の胃がん、食道胃接合部がん又は食道腺がんの成人患者の一次治療を適応とする。 肝細胞がん OPDIVOは、イピリムマブとの併用療法として、切除不能又は進行性の肝細胞がんの成人患者の一次治療を適応とする。
用法・用量	PD-L1 発現状況の検査 適応で特定されている場合には、がん細胞における PD-L1 発現状況をもとにした OPDIVO の投与患者の選択は、CE マークが付与された *in vitro* IVD 医療機器検査により評価する必要がある。CE マークが付与された IVD が利用できない場合、検証された代替検査を使用する必要がある（4.1、4.4 及び 5.1 項参照）。 MSI/MMR 検査

適応で特定されている場合には、MSI-H/dMMR の腫瘍の状態をもとにした OPDIVO の投与患者の選択は、該当する使用目的に合わせて CE マークが付与された IVD により評価する必要がある。CE マークが付与された IVD が利用できない場合は、検証された代替検査を使用する必要がある（4.1 項、4.4 項及び 5.1 項参照）。

用法・用量

OPDIVO 単剤療法

OPDIVO の推奨用量は表 1 に示すとおり、適応症及び投与集団（5.1 項及び 5.2 項参照）に応じてニボルマブ 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔である。

表 1：ニボルマブ単剤静脈内投与時の推奨用量及び点滴時間

適応症*	推奨用量及び点滴時間
悪性黒色腫（進行性又は術後補助療法）	成人及び青年（12 歳以上で体重 50 kg 以上）： 240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 60 分又は 30 分かけて （悪性黒色腫に対する術後補助療法については、5.1 項参照）
	青年（12 歳以上で体重 50 kg 未満）： 3 mg/kg を 2 週間間隔で 30 分かけて、又は 6 mg/kg を 4 週間間隔で 60 分かけて
腎細胞がん 筋層浸潤性尿路上皮がん（MIUC）（術後補助療法）	240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 60 分かけて
食道がん又は食道胃接合部がん（術後補助療法）	最初の 16 週間は 240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 30 分かけて投与し、その後は 480 mg を 4 週間間隔で 30 分かけて投与
非小細胞肺がん 古典的ホジキンリンパ腫 頭頸部扁平上皮がん 尿路上皮がん 食道扁平上皮がん	240 mg を 2 週間間隔で 30 分かけて

*4.1 項の単剤療法の適応に従う。

悪性黒色腫、RCC、OC、GEJC 又は MIUC（術後補助療法）患者の投与計画を 240 mg 2 週間間隔投与から 480 mg 4 週間間隔投与に変更する必要がある場合、最初の 480 mg 投与は最後の 240 mg 投与から 2 週間後に行うこと。逆に、患者が 480 mg 4 週間間隔投与から 240 mg 2 週間間隔投与に切り替える必要がある場合、最初の 240 mg の投与は最後の 480 mg の投与から 4 週間後に行うこと。

OPDIVO 及びイピリムマブ併用療法

悪性黒色腫

成人及び 12 歳以上で体重が 50 kg 以上の青年では、推奨用量として、最初の 4 回の投与ではニボルマブ 1 mg/kg を、また、併用でイピリムマブ 3 mg/kg をそれぞれ 3 週間間隔で点滴静注する。その後第 2 段階として、表 2 に示すとおり、ニボルマブ 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔（5.1 項及び 5.2 項参照）で点滴静注する。ニボルマブ単剤療法の初回投与は、

- 240 mg を 2 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 3 週間後に実施する。又は、
- 480 mg を 4 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 6 週間後に実施する。

12 歳以上で体重が 50 kg 未満の青年では、推奨用量として、最初の 4 回の投与ではニボルマブ 1 mg/kg を、また、併用でイピリムマブ 3 mg/kg をそれぞれ 3 週間間隔で点滴静注する。その後第 2 段階として、表 2 に示すとおり、ニボルマブ 3 mg/kg を 2 週間間隔又は 6 mg/kg を 4 週間間隔（5.1 項及び 5.2 項参照）で点滴静注する。ニボルマブ単剤療法の初回投与は、

- 3 mg/kg を 2 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 3 週間後に実施する。又は、
- 6 mg/kg を 4 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 6 週間後に実施する。

表 2：イピリムマブ併用時の悪性黒色腫に対するニボルマブ静脈内投与時の推奨用量及び点滴時間

	併用投与期、 3 週間間隔、4 サイクル	単剤療法期
ニボルマブ	成人及び 12 歳以上の青年： 1 mg/kg を 30 分かけて投与	成人及び青年（12 歳以上で体重 50 kg 以上）：

		240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 60 分かけて 青年（12 歳以上で体重 50 kg 未満）： 3 mg/kg を 2 週間間隔で 30 分かけて、又は 6 mg/kg を 4 週間間隔で 60 分かけて
イピリムマブ	成人及び 12 歳以上の青年： 3 mg/kg を 30 分かけて投与	－

悪性胸膜中皮腫

推奨用量として、ニボルマブ 360 mg を 3 週間間隔で 30 分かけて、また、併用でイピリムマブ 1 mg/kg を 6 週間間隔で 30 分かけて点滴静注する。病勢進行が認められない患者では、最長 24 カ月間、投与を継続する。

腎細胞がん

推奨用量として、最初の 4 回の投与ではニボルマブ 3 mg/kg を、また、併用でイピリムマブ 1 mg/kg をそれぞれ 3 週間間隔で点滴静注する。その後第 2 段階として、表 3 に示すとおり、ニボルマブ 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔で点滴静注する。ニボルマブ単剤療法の初回投与は、

- 240 mg を 2 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 3 週間後に実施する。又は、
- 480 mg を 4 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 6 週間後に実施する。

表 3：イピリムマブ併用時の RCC に対するニボルマブ静脈内投与の推奨用量及び点滴時間

	併用投与期、 3 週間間隔、4 サイクル	**単剤療法期**
ニボルマブ	3 mg/kg を 30 分かけて投与	240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 60 分かけて
イピリムマブ	1 mg/kg を 30 分かけて投与	－

dMMR 又は MSI-H を有する結腸・直腸がん

表 4 に示すとおり、dMMR 又は MSI-H CRC の一次治療では、推奨用量として、ニボルマブ 240 mg を、また、併用でイピリムマブ 1 mg/kg をそれぞれ 3 週間間隔で最大 4 回点滴静注し、その後ニボルマブ 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔で点滴静注する。ニボルマブ単剤療法の初回投与は、ニボルマブ及びイピリムマブの併用療法の最終投与から 3 週間後に実施する。ニボルマブは、病勢進行、許容できない毒性発現まで投与を継続、又は病勢進行が認められない患者では最長 24 カ月間の投与が推奨される。

表 4 に示すとおり、dMMR 又は MSI-H CRC に対してフルオロピリミジン製剤を含む併用化学療法による前治療後の患者では、推奨用量として、最初の 4 回の投与ではニボルマブ 3 mg/kg を、また、併用でイピリムマブ 1 mg/kg をそれぞれ 3 週間間隔で点滴静注し、その後ニボルマブ 240 mg を 2 週間間隔で点滴静注する。ニボルマブ単剤療法の初回投与は、ニボルマブ及びイピリムマブの併用療法の最終投与から 3 週間後に実施する。

表 4：イピリムマブ併用時の dMMR 又は MSI-H を有する CRC に対するニボルマブ静脈内投与の推奨用量及び点滴時間

		併用投与期、 3 週間間隔、4 サイクル	**単剤療法期**
ニボルマブ	一次治療	240 mg を 30 分かけて投与	240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 30 分かけて
	フルオロピリミジン製剤を含む併用化学療法後	3 mg/kg を 30 分かけて投与	240 mg を 2 週間間隔で 30 分かけて
イピリムマブ		1 mg/kg を 30 分かけて投与	－

食道扁平上皮がん

推奨用量として、ニボルマブ 3 mg/kg を 2 週間間隔又は 360 mg を 3 週間間隔で 30 分かけて点滴静注、また、併用でイピリムマブ 1 mg/kg を 6 週間間隔で 30 分かけて点滴静注する。病勢進行、許容できない毒性発現まで投与を継続、又は病勢進行が認められない患者では最長 24 カ月間の投与が推奨される。

肝細胞がん

推奨用量として、ニボルマブ 1 mg/kg 及びイピリムマブ 3 mg/kg を 3 週間間隔で最大 4 回点滴静注する。その後第 2 段階として、表 5 に示すとおり、ニボルマブ 240 mg を 2 週間間隔**又は** 480 mg を 4 週間間隔（5.1 項及び 5.2 項参照）で点滴静注する。病勢進行、許容できない毒性発現まで投与を継続、又は最長 24 カ月間の投与が推奨される。ニボルマブ単剤療法の初回投与は、

- 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔で投与する場合、ニボルマブ及びイピリムマブの併用療法の最終投与から 3 週間後に実施する。

表 5：イピリムマブ併用時の HCC に対するニボルマブ静脈内投与の推奨用量及び点滴時間

	併用投与期、 3 週間間隔、4 サイクル	**単剤療法期**
ニボルマブ	1 mg/kg を 30 分かけて投与	240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 30 分かけて
イピリムマブ	3 mg/kg を 30 分かけて投与	－

OPDIVO 及びカボザンチニブ併用療法
腎細胞がん
推奨用量として、ニボルマブ 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔で点滴静注、また、併用でカボザンチニブ 40 mg を連日経口投与する。

表 6：カボザンチニブ経口投与と併用時の RCC に対するニボルマブ静脈内投与時の推奨用量及び点滴時間

	併用投与期
ニボルマブ	240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 60 分かけて
カボザンチニブ	1 日 1 回 40 mg

OPDIVO 及びイピリムマブと化学療法併用療法
非小細胞肺がん
推奨用量として、ニボルマブ 360 mg を 3 週間間隔で 30 分かけて、また、併用でイピリムマブ 1 mg/kg を 6 週間間隔で 30 分かけて点滴静注し、プラチナ製剤を含む化学療法を 3 週間間隔で投与する。化学療法 2 サイクル後、ニボルマブ 360 mg を 3 週間間隔で、また、併用でイピリムマブ 1 mg/kg を 6 週間間隔で点滴静注を継続する。病勢進行、許容できない毒性発現まで投与を継続、又は病勢進行が認められない患者では最長 24 カ月間の投与が推奨される。

OPDIVO 及び化学療法併用療法
非小細胞肺がんに対する術前補助療法
推奨用量として、ニボルマブ 360 mg を 30 分かけて点滴静注を、プラチナ製剤を含む化学療法と併用し、3 週間間隔で 3 サイクル実施する（5.1 項参照）。

非小細胞肺がんに対する術前及び術後補助療法
推奨用量として、術前補助療法期にニボルマブ 360 mg を 30 分かけて点滴静注を、プラチナ製剤を含む化学療法と併用し、3 週間間隔で 4 サイクル実施し、その後術後補助療法としてニボルマブ 480 mg を 4 週間間隔で点滴静注する。病勢進行、再発、許容できない毒性発現まで投与を継続、又は最長 13 サイクルの投与が推奨される（5.1 項参照）。

食道扁平上皮がん
推奨用量として、ニボルマブ 240 mg を 2 週間間隔又は 480 mg を 4 週間間隔で 30 分かけて点滴静注を、フルオロピリミジン及びプラチナ製剤を含む化学療法と併用する（5.1 項参照）。ニボルマブは、病勢進行、許容できない毒性発現まで投与を継続、又は病勢進行が認められない患者では最長 24 カ月間の投与が推奨される。

胃がん、食道胃接合部がん又は食道腺がん
推奨用量として、ニボルマブ 360 mg を 30 分かけて点滴静注を、フルオロピリミジン及びプラチナ製剤を含む化学療法と併用し、3 週間間隔で実施する。又は、ニボルマブ 240 mg を 30 分かけて点滴静注を、フルオロピリミジン及びプラチナ製剤を含む化学療法と併用し、2 週間間隔で実施する（5.1 項参照）。ニボルマブは、病勢進行、許容できない毒性発現まで投与を継続、又は病勢進行が認められない患者では最長 24 カ月間の投与が推奨される。

切除不能又は転移性尿路上皮がんに対する一次治療
推奨用量として、ニボルマブ 360 mg を 30 分かけて点滴静注を、シスプラチン及びゲムシタビンと併用し、3 週間間隔で最大 6 サイクル実施した後、ニボルマブ 240 mg を 2 週間間隔で 30 分かけて、又は 480 mg を 4 週間間隔で 30 分かけて点滴静注で単剤投与する（5.1 項参照）。ニボルマブは、病勢進行、許容できない毒性発現又は初回投与から最長 24 カ月のいずれか早い時点までの投与が推奨される。

	投与期間 単剤療法又はイピリムマブ若しくは他の治療薬との併用療法のいずれにおいても、OPDIVO の投与は、臨床的有益性が認められる限り継続するか、患者が忍容性を示さなくなるまで継続する（適応症に対して指定されている場合は最長治療期間）。 術後補助療法に対する OPDIVO の最長投与期間は 12 カ月である。 OPDIVO をカボザンチニブと併用する場合、OPDIVO は病勢進行、許容できない毒性発現まで投与を継続、又は疾病勢進行が認められない患者では最長 24 カ月間の投与が推奨される。カボザンチニブは病勢進行、許容できない毒性発現まで投与を継続することが推奨される。カボザンチニブの欧州製品概要（SmPC）を参照すること。 非定型の反応（初期の一時的な腫瘍サイズの増大又は最初の数カ月の小さな新規病変の発現、その後腫瘍の縮小が認められる）が認められた。病勢進行の最初のエビデンスを示した、臨床的に安定している患者については、病勢進行が確認されるまでニボルマブ又はニボルマブとイピリムマブとの併用投与を継続することを推奨する。
禁忌	有効成分又は 6.1 項に一覧表示する添加物に対して過敏症のある患者
警告及び使用上の注意	<u>トレーサビリティ</u> 生物学的製剤のトレーサビリティを向上させるために、投与された製品の名称及びロット番号を明確に記録すること。 <u>PD-L1 発現状況の評価</u> 腫瘍の PD-L1 発現状況を評価する際には、十分に検証された頑健な方法を用いることが重要である。 <u>MSI/MMR 発現状況の評価</u> 腫瘍の MSI-H 及び dMMR 発現状況を評価する際には、十分に検証された頑健な方法を用いることが重要である。 <u>免疫に関連した副作用</u> ニボルマブを併用投与する際は、投与の開始前に他の併用治療薬の製品概要を参照すること。免疫に関連した副作用は、ニボルマブの単剤療法と比較して、ニボルマブ及びイピリムマブの併用療法時に高頻度で発現した。ニボルマブ及びカボザンチニブの併用療法時の免疫に関連した副作用発現頻度は、ニボルマブの単剤療法と同程度であった。したがって、特に明記されている場合を除き、免疫に関連した副作用に関する以下のガイダンスは、併用療法の場合の OPDIVO にも適用される。ほとんどの免疫に関連した副作用は、副腎皮質ステロイドの投与開始や用量調節などの適切な管理により改善又は消失した（4.2 項参照）。 複数の器官に影響を及ぼす免疫に関連した副作用が同時に発現する可能性がある。 肺塞栓症を含む心臓及び肺の副作用も併用療法で報告されている。投与前及び投与期間中は定期的に、心臓及び肺の副作用、並びに電解質異常及び脱水を示唆する臨床的徴候、症状及び臨床検査値異常について、患者を継続的にモニタリングする。ニボルマブ及びイピリムマブの併用投与は、生命を脅かす又は再発の重度の心臓及び肺の副作用が発現した場合は中止する（4.2 項参照）。 ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与に対する副作用は、投与期間中又は投与中止後のいかなる時点でも発現する可能性があるため、患者を継続して（少なくとも最終投与日から 5 カ月まで）モニタリングすること。 免疫に関連した副作用が疑われる場合、病因を特定するため又は他の原因を除外するために、適切な検査を実施する。副作用の重症度に基づいて、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、副腎皮質ステロイドの投与を開始する。副作用の治療に副腎皮質ステロイドによる免疫抑制を利用した場合、副作用が改善したら、副腎皮質ステロイドを 1 カ月以上かけて漸減する。副腎皮質ステロイドを急に減量すると、副作用が悪化又は再発するおそれがある。副腎皮質ステロイドを投与しても副作用が悪化する又は改善しない場合、他の免疫抑制剤を追加投与する。 自己免疫疾患（AID）の既往歴を有する患者では、免疫チェックポイント阻害剤による治療後の免疫に関連した副作用のリスクが、AID の既往歴のない患者と比較して上昇する可能性があることが、観察研究のデータから示唆されている。また、基礎疾患である AID の再燃が高頻度に認められたが、大部分は軽度で管理可能であった。 副腎皮質ステロイド又は他の免疫抑制剤を投与中の場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開してはならない。免疫抑制剤を投与中の患者に対して、日和見感染症を防ぐために抗生物質の予防投与を実施する。 重度の免疫に関連した副作用が再発した場合、及び生命を脅かす免疫に関連した副作用が発現した場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。

	免疫に関連した肺臓炎 ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与により、重度の肺臓炎又は間質性肺疾患（死亡例を含む）が認められている（4.8 項参照）。放射線学的変化（例：限局性すりガラス様陰影像、斑状浸潤像）、呼吸困難、低酸素症などの肺臓炎の徴候及び症状をモニタリングすること。感染及び原疾患は原因から除外する。 Grade 3 又は Grade 4 の肺臓炎が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止し、副腎皮質ステロイドの投与を 2～4 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。 Grade 2 の（症候性の）肺臓炎が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、副腎皮質ステロイドの投与を 1 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。肺臓炎が改善したら、副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開することができる。副腎皮質ステロイドの投与を開始しても肺臓炎が悪化する又は改善しない場合、副腎皮質ステロイドの用量を 2～4 mg/kg/日（メチルプレドニゾロン換算）に増量し、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。 *免疫に関連した大腸炎* ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与により、重度の下痢又は大腸炎が認められている（4.8 項参照）。下痢と、大腸炎の随伴症状（腹痛、便中の粘液、血便など）をモニタリングする。感染及び原疾患は原因から除外する。サイトメガロウイルス（CMV）感染／再活性化は、副腎皮質ステロイド抵抗性の免疫に関連した大腸炎の患者で報告されている。感染症をはじめとする下痢の病因を除外する必要があるため、適切な臨床検査及び追加検査を実施しなければならない。副腎皮質ステロイド抵抗性の免疫に関連した大腸炎の診断が確定した場合、副腎皮質ステロイド療法に対する代替免疫抑制剤の追加又は副腎皮質ステロイド療法の代替を考慮すること。 Grade 4 の下痢又は大腸炎が認められた場合、ニボルマブ単剤療法又はニボルマブ及びイピリムマブの併用投与を永続的に中止し、副腎皮質ステロイドの投与を 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。 Grade 3 の下痢又は大腸炎が認められた場合、ニボルマブ単剤投与を中断し、副腎皮質ステロイドの投与を 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。下痢又は大腸炎が改善したら、副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与を再開することができる。副腎皮質ステロイドの投与を開始しても下痢又は大腸炎が悪化する又は改善しない場合、ニボルマブ単剤投与を永続的に中止する。ニボルマブ及びイピリムマブの併用投与で Grade 3 の下痢又は大腸炎が認められた場合、併用投与を永続的に中止し、副腎皮質ステロイドの投与を 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。 Grade 2 の下痢又は大腸炎が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断する。下痢又は大腸炎が持続する場合、副腎皮質ステロイドの投与を 0.5～1 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。下痢又は大腸炎が改善したら、必要とした場合には副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開することができる。副腎皮質ステロイドの投与を開始しても下痢又は大腸炎が悪化する又は改善しない場合、副腎皮質ステロイドの用量を 1～2 mg/kg/日（メチルプレドニゾロン換算）に増量し、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。 *免疫に関連した肝炎* ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与により、重度の肝炎が認められている（4.8 項参照）。トランスアミナーゼ及び総ビリルビンの増加などの肝炎の徴候及び症状をモニタリングする。感染及び原疾患は原因から除外する。 Grade 3 又は Grade 4 のトランスアミナーゼ又は総ビリルビンの増加が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止し、副腎皮質ステロイドの投与を 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。 Grade 2 のトランスアミナーゼ又は総ビリルビンの増加が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断する。これらの臨床検査値の上昇が持続する場合、副腎皮質ステロイドの投与を 0.5～1 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。これらの臨床検査値が改善したら、必要とした場合には副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開することができる。副腎皮質ステロイドの投与を開始してもこれらの臨床検査値が悪化する又は改善しない場合、副腎皮質ステロイドの用量を 1～2 mg/kg/日（メチルプレドニゾロン換算）に増量し、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。

	免疫に関連した腎炎又は腎機能障害 ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与により、重度の腎炎又は腎機能障害が認められている（4.8 項参照）。腎炎及び腎機能障害の徴候及び症状をモニタリングする。大半の患者は症状を伴わない血清クレアチニン増加を呈する。原疾患は原因から除外する。 Grade 4 の血清クレアチニン増加が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止し、副腎皮質ステロイドの投与を 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。 Grade 2 又は Grade 3 の血清クレアチニン増加が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、副腎皮質ステロイドの投与を 0.5～1 mg/kg/日（メチルプレドニゾロン換算）の用量で開始する。血清クレアチニン値が改善したら、副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開することができる。副腎皮質ステロイドの投与を開始しても血清クレアチニン値が悪化する又は改善しない場合、副腎皮質ステロイドの用量を 1～2 mg/kg/日（メチルプレドニゾロン換算）に増量し、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。 *免疫に関連した内分泌障害* ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与により、重度の内分泌障害（甲状腺機能低下症、甲状腺機能亢進症、副腎機能不全［続発性副腎皮質機能不全を含む］、下垂体炎［下垂体機能低下症を含む］、糖尿病、糖尿病性ケトアシドーシスを含む）が認められている（4.8 項参照）。 内分泌障害の臨床徴候及び症状、高血糖、並びに甲状腺機能の変化（投与開始時、投与期間中の定期的な時点及び臨床評価に基づいて適宜）についてモニタリングする。患者は、疲労、頭痛、精神状態変化、腹痛、便習慣変化及び低血圧を呈したり、脳転移又は基礎疾患などの他の原因による症状と類似する非特異的な症状を呈したりすることがある。他の原因が特定されない限り、内分泌障害の徴候又は症状は免疫に関連するものと判断される。 症候性の甲状腺機能低下症が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、必要に応じて甲状腺ホルモンの補充投与を開始する。症候性の甲状腺機能亢進症が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、必要に応じて抗甲状腺薬の投与を開始する。甲状腺の急性炎症が疑われる場合、副腎皮質ステロイドを 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で投与することも検討する。甲状腺の急性炎症が改善したら、必要とした場合には副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開することができる。甲状腺機能のモニタリングを継続し、ホルモン補充が適切に行われていることを確認する。生命を脅かす甲状腺機能亢進症又は甲状腺機能低下症が認められた場合は、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。 症候性の Grade 2 の副腎機能不全が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、必要に応じて生理的な副腎皮質ステロイドの補充投与を開始する。重度（Grade 3）又は生命を脅かす（Grade 4）副腎機能不全が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。副腎の機能及びホルモン値のモニタリングを継続し、副腎皮質ステロイドの補充が適切に行われていることを確認する。 症候性の Grade 2 又は Grade 3 の下垂体炎が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、必要に応じてホルモンの補充投与を開始する。下垂体の急性炎症が疑われる場合、副腎皮質ステロイドを 1～2 mg/kg/日（メチルプレドニゾロン換算）の用量で投与することも検討する。下垂体の急性炎症が改善したら、必要とした場合には副腎皮質ステロイドを漸減してから、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を再開することができる。生命を脅かす（Grade 4）下垂体炎が認められた場合は、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。下垂体の機能及びホルモン値のモニタリングを継続し、ホルモン補充が適切に行われていることを確認する。 症候性の糖尿病が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、必要に応じてインスリンの補充投与を開始する。血糖値のモニタリングを継続し、インスリン補充が適切に行われていることを確認する。生命を脅かす糖尿病が認められた場合は、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。 *免疫に関連した皮膚の副作用* ニボルマブ及びイピリムマブの併用投与により、また発現頻度は低いがニボルマブ単剤投与でも、重度の発疹が認められている（4.8 項参照）。Grade 3 の発疹が認められた場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、Grade 4 の発疹が認められた場合、投与を中止する。重度の発疹が認められた場合、高用量の副腎皮質ステロイド 1～2 mg/kg/日（プレドニゾン換算）を投与する。

	死亡に至る例も含む SJS 及び TEN もまれに認められている。SJS 又は TEN の兆候又は症状が認められた場合は、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中止し、評価及び治療のために患者を専門部署に移す。ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与により、患者が SJS 又は TEN を発現した場合は、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与の永続的な中止が推奨される（4.2 項参照）。 免疫賦活性の他の抗がん剤による前治療で重度又は生命を脅かす皮膚の副作用が発現したことのある患者では、ニボルマブの使用を慎重に検討する必要がある。 *その他の免疫に関連した副作用* 各用量及び各がん腫を対象とした臨床試験において、以下の免疫に関連した副作用が、ニボルマブ単剤投与又はニボルマブとイピリムマブの併用投与を受けた患者の 1%未満に報告された。膵炎、ぶどう膜炎、脱髄、自己免疫性ニューロパチー（顔面神経不全麻痺及び外転神経不全麻痺を含む）、ギラン・バレー症候群、重症筋無力症、筋無力症候群、無菌性髄膜炎、脳炎、胃炎、サルコイドーシス、十二指腸炎、筋炎、心筋炎、横紋筋融解症及び脊髄炎。また、フォークト・小柳・原田症候群、副甲状腺機能低下症及び非感染性膀胱炎の症例が市販後に報告されている（4.2 項及び 4.8 項参照）。 免疫に関連した副作用が疑われる場合、原因を特定するため又は他の原因を除外するために、適切な検査を実施する。副作用の重症度に基づいて、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断し、副腎皮質ステロイドの投与を開始する。副作用が改善したら、副腎皮質ステロイドを漸減してから、本剤の投与を再開することができる。重度の免疫に関連した副作用が再発した場合、及び生命を脅かす免疫に関連した副作用が発現した場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を永続的に中止する。 死亡転帰を含む筋毒性（筋炎、心筋炎及び横紋筋融解症）が、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与で報告されている。筋毒性の兆候又は症状が認められた場合は、厳格なモニタリングを実施し、評価及び治療のために遅滞なく患者を専門部署に移す。筋毒性の重症度に基づいて、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断又は中止し（4.2 項参照）、適切な治療を開始する。 心筋炎の診断には、強く疑う必要がある。心臓又は心肺に症状のある患者では、心筋炎の可能性について評価すべきである。心筋炎が疑われる場合は、高用量ステロイド（プレドニゾン 1～2 mg/kg/日又はメチルプレドニゾロン 1～2 mg/kg/日）の投与を速やかに開始し、最新の臨床ガイドラインに従った精密検査による心臓病専門医へのコンサルテーションを速やかに開始する。心筋炎の診断が確定した場合、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中断又は永続的に中止すること（4.2 項参照）。 市販後の調査で、PD-1 阻害剤の投与を受けている患者で、固形臓器移植による拒絶反応が報告されている。ニボルマブの投与により、固形臓器移植者の拒絶反応のリスクが増加する可能性がある。これらの患者については、ニボルマブ投与によるベネフィットと臓器移植の拒絶反応のリスクの可能性を比較検討する必要がある。 ニボルマブ単剤投与又はニボルマブとイピリムマブの併用投与により、血球貪食性リンパ組織球症（HLH）が認められている。ニボルマブを単独投与又はイピリムマブと併用投与する場合は注意が必要である。HLH が確認された場合は、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を中止し、HLH の治療を開始すること。 <u>注入に伴う反応</u> ニボルマブ又はニボルマブ及びイピリムマブの併用投与の臨床試験において重度の注入に伴う反応が報告されている（4.8 項参照）。重度又は生命を脅かす注入に伴う反応が認められた場合、本剤の投与を中止し、適切な医学的処置を行う。軽度又は中等度の注入に伴う反応が発現した患者では、厳格なモニタリングの下に、及び注入に伴う反応予防のための局所的治療ガイドラインに従った前投薬により、ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用投与を実施することができる。 <u>疾患特異的な使用上の注意</u> *<u>進行性悪性黒色腫</u>* ベースラインの Performance Status（PS）スコアが 2 以上の患者、活動性脳転移又は髄膜転移、自己免疫疾患を有する患者、及び試験登録前に全身免疫抑制剤を投与されていた患者は、ニボルマブ単剤療法又はニボルマブ及びイピリムマブの併用療法の主たる臨床試験から除外した（4.5 項及び 5.1 項参照）。また、眼球／ぶどう膜黒色腫を有する患者は、悪性黒色腫の主たる臨床試験から除外した。さらに、CA209037 試験では、抗 CTLA-4 療法と関連する Grade 4 の副作用が発現したことのある患者を除外した（5.1 項参照）。ベースライン時の Performance Status スコアが 2 で、髄膜転移、眼球／ぶどう膜黒色腫、自己免疫疾患の治療を受けた患者及び以前に受けた抗 CTLA-4 療法に関連する Grade 3-4 の副作用が発現した患者を CA209172 試験に組み入れた（5.1 項参照）。試験登録前に免疫抑制剤の全身投与を受けていた患者、並びに活動性の脳転移又は髄

	膜転移を有する患者に関するデータが得られていないことから、このような患者に対する本剤の使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 ニボルマブ単剤投与と比較して、ニボルマブ及びイピリムマブの併用投与の無増悪生存期間（PFS）の延長は、PD-L1 発現率の低い患者のみで確立されている。OS の改善は、PD-L1 発現率の高い患者（PD-L1 発現率 1%以上）においてはニボルマブ及びイピリムマブの併用投与、ニボルマブ単剤投与とも同程度であった。併用投与を開始する前に、医師にはニボルマブ単剤投与と比較して、併用投与のベネフィット及び毒性を考慮に入れ、各患者及び腫瘍の特性を注意深く評価するよう推奨する（4.8 項及び 5.1 項参照）。 *急速な病勢進行を呈する悪性黒色腫患者に対するニボルマブの投与* 急速な病勢進行を呈する悪性黒色腫患者に対してニボルマブの投与を開始するにあたり、医師は本剤の効果発現が遅いことを考慮する必要がある（5.1 項参照）。 *悪性黒色腫の術後補助療法* 以下の危険因子（4.5 項及び 5.1 項参照）を有する悪性黒色腫患者に対する術後補助療法に関するデータはない。 • 自己免疫疾患の既往があり、副腎皮質ステロイド（10 mg/日以上のプレドニゾン又は同換算量）又はその他の免疫抑制剤の全身投与を必要とする患者 • 悪性黒色腫の治療歴（ただし、手術を受けた患者、中枢神経系病変に対する神経外科的切除後の術後補助放射線療法を受けた患者及びランダム化の 6 カ月以上前に術後補助インターフェロン療法を受けた患者を除く）を有する患者 • 抗 PD-1 抗体、抗 PD-L1 抗体、抗 PD-L2 抗体、抗 CD 137 抗体又は抗 CTLA-4 抗体による前治療歴のある患者（イピリムマブ又は T 細胞共刺激経路又はチェックポイント経路を特異的に標的とするその他の抗体又は薬剤を含む） • 18 歳未満の被験者 データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *非小細胞肺がん* *NSCLC の一次治療* 活動性自己免疫疾患、症候性の間質性肺疾患、全身性免疫抑制を必要とする医学的状態、活動性（未治療）脳転移を有する患者、進行疾患に対する全身治療歴がある患者、EGFR 変異又は ALK 転座に感作が認められる患者は、NSCLC の一次治療を検討する主たる試験から除外した（4.5 項及び 5.1 項参照）。高齢患者（75 歳以上）のデータは限られている（5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブとイピリムマブ及び化学療法の併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *化学療法後の NSCLC の治療* ベースラインの Performance Status（PS）スコアが 2 以上の患者、活動性脳転移又は自己免疫疾患を有する患者、症候性の間質性肺疾患を有する患者、及び試験登録前に全身免疫抑制剤を投与されていた患者は、NSCLC の主たる臨床試験から除外した（4.5 項及び 5.1 項参照）。ベースラインの Performance Status スコアが 2 の患者を CA209171 試験に組み入れた（5.1 項参照）。自己免疫疾患、症候性の間質性肺疾患及び活動性脳転移を有する患者、並びに試験登録前に免疫抑制剤の全身投与を受けていた患者に関するデータが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 予後不良の疾患又は悪性度の高い疾患、若しくはその両方を有する患者に対してニボルマブの投与を開始するにあたり、医師は本剤の効果発現が遅いことを考慮する必要がある。非扁平上皮 NSCLC 患者において、ドセタキセル投与群と比較してニボルマブ投与群で 3 カ月以内の高い死亡率が認められた。早期死亡に関連する要因としては、PD-L1 発現状況が低い又はなしであることとあわせて、予後不良因子又は悪性度の高い疾患、若しくはその両方などが挙げられる（5.1 項参照）。 *NSCLC の術前補助療法* ベースラインの Performance Status（PS）スコアが 2 以上の患者、活動性自己免疫疾患を有する患者、症候性の間質性肺疾患を有する患者、全身免疫抑制を要する医学的状態の患者、切除不能又は転移性病変を有する患者、切除可能な病変への抗がん治療の前治療を受けた患者、EGFR 変異又は ALK 転座陽性の患者は、切除可能な NSCLC に対する術前補助療法の主たる試験から除外した（5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブと化学療法の併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *非小細胞肺がんの術前及び術後補助療法*

	ベースラインの Performance Status（PS）スコアが 2 以上の患者、Grade 2 以上の末梢性ニューロパチーを有する患者、活動性自己免疫疾患を有する患者、症候性の間質性肺疾患を有する患者、全身免疫抑制を要する医学的状態の患者、切除不能又は転移性病変を有する患者、切除可能な病変への抗がん治療の前治療を受けた患者、EGFR 変異又は ALK 転座陽性の患者、脳転移を有する患者は、NSCLC に対する術前及び術後補助療法の主たる試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブと化学療法の併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *悪性胸膜中皮腫* 腹膜原発、心膜原発、精巣原発又は精巣鞘膜原発の中皮腫を有する患者、間質性肺疾患を有する患者、活動性自己免疫疾患を有する患者、全身免疫抑制を要する医学的状態の患者及び脳転移を有する患者（外科的な切除又は定位放射線治療による治療を受け、組入れ前の 3 カ月以内に進展を認めない場合を除く）は、MPM の一次治療を検討する主たる試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブとイピリムマブの併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *腎細胞がん* *ニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用療法* 脳転移の既往歴又は併発症を有する患者、活動性の自己免疫疾患を有する患者、又は全身免疫抑制を要する医学的状態の患者はニボルマブ単剤投与又はニボルマブ及びイピリムマブの併用療法の試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブ又はニボルマブ及びイピリムマブの併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *ニボルマブ単剤投与又はニボルマブ及びカボザンチニブの併用療法* 活動性の脳転移、自己免疫疾患を有する患者、又は全身免疫抑制を要する医学的状態の患者はニボルマブ単剤投与又はニボルマブ及びカボザンチニブの併用療法の試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブ及びカボザンチニブの併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 ニボルマブをカボザンチニブと併用投与した場合、進行 RCC 患者での Grade 3 及び 4 の ALT 及び AST 増加の発現頻度はニボルマブ単剤投与時よりも高かった（4.8 項参照）。投与開始前及び投与期間を通じて定期的に肝酵素をモニタリングすること。両薬剤の医学的管理ガイドラインに従うこと（4.2 項及びカボザンチニブの SmPC を参照のこと）。 *古典的ホジキンリンパ腫* 活動性の自己免疫疾患及び症候性の間質性肺疾患を有する患者は cHL の臨床試験から除外した（5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *古典的ホジキンリンパ腫患者における同種造血幹細胞移植（HSCT）の合併症* ニボルマブ投与後に同種 HSCT を受けた患者の追跡調査より、急性移植片対宿主病（GVHD）症例及び移植関連死亡（TRM）例が認められている。HSCT の潜在的なベネフィットと移植関連の合併症のリスク増加の可能性について、個々の症例に応じて慎重に検討すること（4.8 項参照）。 製造販売後において、同種 HSCT 後にニボルマブを投与した患者で、死亡例を含む急速発症型の重度の GVHD が報告されている。ニボルマブの投与は、主に GVHD の既往を有する患者において、同種 HSCT 施行後の重症 GVHD 及び死亡のリスクを上昇させる可能性があることから、このような患者では、ニボルマブの使用は、潜在的なリスクとベネフィットを検討すること（4.8 項参照）。 *頭頸部がん* ベースラインの Performance Status（PS）スコアが 2 以上の患者、活動性の脳又は軟膜・髄膜転移を有する患者、活動性の自己免疫疾患を有する患者、全身免疫抑制を要する医学的状態の患者、又は原発部位として鼻咽頭がん若しくは唾液腺がんを有する患者は SCCHN の臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 予後不良の疾患又は悪性度の高い疾患、若しくはその両方を有する患者に対してニボルマブの投与を開始するにあたり、医師は本剤の効果発現が遅いことを考慮する必要がある。頭頸部がん患者において、ドセタキセル投与群と比較してニボルマブ投与群で 3 カ月以内の高い死亡率が認められた。早期死亡に関連する要因としては、ECOG Performance Status、プラチナ製剤を含む化学療法による前治療中に速い進行が認められた疾患、及び高腫瘍量などが挙げられる。

	尿路上皮がん *進行性尿路上皮がんの治療* ベースラインの Performance Status（PS）スコアが 2 以上の患者、活動性の脳又は軟膜・髄膜転移を有する患者、活動性の自己免疫疾患を有する患者、又は全身免疫抑制を要する医学的状態の患者は尿路上皮がんの臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *尿路上皮がんの術後補助療法* ベースラインの Performance Status（PS）スコアが 2 以上の患者（シスプラチンを含む術前補助化学療法を受けておらず、シスプラチンの術後補助化学療法に不適応と判定されたベースラインの PS が 2 の患者を除く）、術後に病変が認められた患者、活動性の自己免疫疾患を有する患者又は全身免疫抑制を要する医学的状態の患者は尿路上皮がんに対する術後補助療法の臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *dMMR 又は MSI-H を有する結腸・直腸がん* ベースラインの Performance Status（PS）スコアが 2 以上の患者、活動性の脳又は軟膜・髄膜転移を有する患者、活動性の自己免疫疾患を有する患者又は全身免疫抑制を要する医学的状態の患者は dMMR 又は MSI-H を有する転移性 CRC の臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブとイピリムマブの併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *食道扁平上皮がん* *OSCC の一次治療* ベースラインの Performance Status（PS）スコアが 2 以上の患者、脳転移の併発を認める患者、活動性の自己免疫疾患を有する患者、全身免疫抑制を要する医学的状態の患者又は食道病変の近位器官への明らかな腫瘍浸潤による出血又は瘻孔のリスクが高い患者は OSCC の臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブとイピリムマブ又は化学療法の併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 OSCC の一次治療を評価する試験において、化学療法群と比較してニボルマブとイピリムマブとの併用投与群で 4 カ月以内の死亡例数が高かった。予後不良の背景又は悪性度の高い疾患、若しくはその両方を有する患者に対してニボルマブとイピリムマブの併用投与を開始するにあたり、医師はその効果発現が遅いことを考慮する必要がある（5.1 項参照）。 *一次治療の化学療法後の OSCC の治療* 食道扁平上皮癌で入手可能な臨床データの大部分はアジア人患者のものである（5.1 項参照）。OSCC を対象とした臨床試験では、ベースライン時の Performance Status スコアが 2 以上の患者、症候性又は治療を要する脳転移を有する患者、食道に隣接する臓器への明らかな腫瘍浸潤を有する患者（例：大動脈又は気道）、活動性自己免疫疾患を有する患者又は全身性の免疫抑制を要する医学的状態を有する患者は除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 医師は OSCC 患者では治療開始前にニボルマブの効果の発現が遅いことを考慮する必要がある。ランダム化後 2.5 カ月以内の死亡数はニボルマブ群の方が化学療法群よりも多かった。早期死亡に関連する因子は特定されなかった（5.1 項参照）。 *食道がん又は食道胃接合部がんに対する術後補助療法* ベースラインの Performance Status（PS）スコアが 2 以上の患者、術前に同時化学放射線療法（CRT）を実施してない患者、IV 期の切除可能な病変を有する患者、活動性の自己免疫疾患を有する患者又は全身免疫抑制を要する医学的状態の患者は食道がん又は食道胃接合部がんの臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブの使用は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 *胃がん、食道胃接合部がん又は食道腺がん* ベースラインの ECOG Performance Status（PS）スコアが 2 以上の患者、未治療の中枢神経系転移を有する患者、活動性自己免疫疾患を有する患者、自己免疫疾患が確認されている又は疑われる患者、若しくは全身免疫抑制を要する医学的状態の患者は胃がん、GEJ がん又は食道腺がんの臨床試験から除外した（4.5 項及び 5.1 項参照）。データが得られていないことから、このような患者に対するニボルマブと化学療法の併用投与は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。

	CA209649 試験では、HER2 陽性であることが確認されている患者を除外した。未確定の患者は試験に組み入れられ、患者の 40.3%に相当した（5.1 項参照）。 *肝細胞がん* ベースラインの ECOG Performance Status（PS）スコアが 2 以上の患者、肝移植歴、Child-Pugh 分類 C の肝疾患、脳転移の合併歴、肝性脳症の既往歴（ランダム化前 12 カ月以内）、臨床的に重要な腹水、HIV 感染、B 型肝炎ウイルス（HBV）と C 型肝炎ウイルス（HCV）又は HBV と D 型肝炎ウイルス（HDV）の活動性重複感染、活動性自己免疫疾患又は全身免疫抑制を要する医学的状態の患者は、HCC の臨床試験から除外した（4.5 項及び 5.1 項参照）。Child-Pugh 分類 B の HCC 患者で得られているデータは限られている。データが得られていないことから、このような患者に対するニボルマブとイピリムマブの併用投与後にニボルマブを投与する場合は、患者ごとに潜在的なリスクとベネフィットを慎重に検討した上で注意して行うこと。 肝細胞がんに対するニボルマブとイピリムマブの併用療法では、レンバチニブ又はソラフェニブと比較して、6 カ月以内の死亡が多く認められた。死亡リスクの増加は予後不良の疾患と関連している可能性がある。予後不良の疾患を有する患者に対してニボルマブとイピリムマブの併用療法を開始するにあたり、医師はこのリスクを考慮する必要がある。 <u>ナトリウム管理食を摂取中の患者</u> 本剤は 1 mL 中にナトリウム 0.1 mmol（2.5 mg）を含有する。本剤は、ナトリウム 10 mg/4mL バイアル、ナトリウム 25 mg/10mL バイアル、ナトリウム 30 mg/12mL バイアル又はナトリウム 60 mg/24mL バイアルを含有し、これは WHO が成人に推奨するナトリウム 2 g の最大一日摂取量のそれぞれ 0.5%、1.25%、1.5%又は 3%に相当する。希釈段階で塩化ナトリウムを使用する場合、ナトリウム摂取量が異なる可能性がある。 <u>患者アラートカード</u> OPDIVO の処方者は全員、医師用情報（Physician Information）及び管理ガイドライン（Management Guideline）を熟知していなければならない。処方者は OPDIVO 投与におけるリスクについて患者に説明する必要がある。患者には各処方時に患者アラートカード（Patient Alert Card）を提供する。

1.6.2 企業中核データシート（CCDS）

CCDS の原文を添付した。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPDIVO safely and effectively. See full prescribing information for OPDIVO.

OPDIVO® (nivolumab) injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	5/2025
Dosage and Administration (2)	5/2025

----------INDICATIONS AND USAGE----------

OPDIVO is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

Melanoma

- adult and pediatric (12 years and older) patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab. (1.1)
- for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. (1.2)

Non-Small Cell Lung Cancer (NSCLC)

- adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy. (1.3)
- adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by single-agent OPDIVO as adjuvant treatment after surgery. (1.4)
- adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab. (1.5)
- adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy. (1.5)
- adult patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.5)

Malignant Pleural Mesothelioma

- adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab. (1.6)

Renal Cell Carcinoma (RCC)

- adult patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab. (1.7)
- adult patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib. (1.7)
- adult patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.7)

Classical Hodgkin Lymphoma (cHL)

- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[a]: (1.8)
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.9)

Urothelial Carcinoma

- adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC. (1.10)
- adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine. (1.10)
- adult patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.10)

Colorectal Cancer

- adult and pediatric (12 years and older) patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) in combination with ipilimumab. (1.11)
- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. (1.11)

Hepatocellular Carcinoma (HCC)

- adult patients with unresectable or metastatic hepatocellular carcinoma (HCC), as a first-line treatment in combination with ipilimumab. (1.12)
- in combination with ipilimumab in adult patients with unresectable or metastatic HCC who have been previously treated with sorafenib. (1.12)

Esophageal Cancer

- adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT). (1.13)
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy whose tumors express PD-L1 (≥1). (1.13)
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with ipilimumab whose tumors express PD-L1 (≥1). (1.13)
- adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. (1.13)

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (≥1) in combination with fluoropyrimidine- and platinum-containing chemotherapy. (1.14)

[a] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

----------DOSAGE AND ADMINISTRATION----------

- Administer by intravenous infusion after dilution based upon recommended infusion rate for each indication. (2)
- Unresectable or metastatic melanoma
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. (2.2)
  - Adult and pediatric patients weighing 40 kg or greater: 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. (2.2)
- Adjuvant treatment of melanoma
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. (2.2)
- Neoadjuvant treatment of resectable (tumors ≥4 cm or node positive) non-small cell lung cancer
  - 360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles. (2.2)
- Neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer
  - 360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for up to 4 cycles, then continued as single-agent OPDIVO 480 mg every 4 weeks after surgery for up to 13 cycles (~1 year). (2.2)
- Metastatic non-small cell lung cancer
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Malignant pleural mesothelioma
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
- Advanced renal cell carcinoma
  - 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks administered in combination with cabozantinib 40 mg once daily without food. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Classical Hodgkin lymphoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)

- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Adjuvant treatment of urothelial carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- First-line unresectable or metastatic urothelial carcinoma
  - 360 mg every 3 weeks with cisplatin and gemcitabine on the same day for up to 6 cycles, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Previously treated locally advanced or metastatic urothelial carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for a maximum of 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for a maximum of 4 doses, then 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. (2.2)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following prior treatment for metastatic disease.
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks. (2.2)
- Hepatocellular carcinoma
  - 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Adjuvant treatment of resected esophageal or gastroesophageal cancer
  - 240 mg every 2 weeks or 480 mg every 4 weeks for total treatment duration of 1 year. (2.2)
- Esophageal squamous cell carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks in combination with chemotherapy regimen of fluoropyrimidine- and platinum-containing chemotherapy. (2.2)
  - 3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC, GEJC, or EAC)
  - 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. (2.2)
  - 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks. (2.2)
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) solution in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Immune-Mediated Adverse Reactions: (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, and immune-mediated nephritis and renal dysfunction.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction. (2.3)
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue OPDIVO based on severity of reaction. (5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥20%) in patients were:

- As a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, vomiting, and urinary tract infection. (6.1)
- In combination with ipilimumab: fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, constipation, decreased weight, and dizziness. (6.1)
- In combination with platinum-doublet chemotherapy: nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy. (6.1)
- In combination with ipilimumab and platinum-doublet chemotherapy: fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (6.1)
- In combination with cabozantinib: diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection. (6.1)
- In combination with fluoropyrimidine- and platinum-containing chemotherapy: nausea, peripheral neuropathy, decreased appetite, fatigue, constipation, stomatitis, diarrhea, vomiting, abdominal pain, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

1.2 Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

1.3 Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

1.4 Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO as adjuvant treatment after surgery.

1.5 Metastatic Non-Small Cell Lung Cancer

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations.
- OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.
- OPDIVO is indicated for the treatment of adult patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

1.6 Malignant Pleural Mesothelioma

OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

1.7 Advanced Renal Cell Carcinoma

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced RCC.

- OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.
- OPDIVO, as a single agent, is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

1.8 Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.9 Squamous Cell Carcinoma of the Head and Neck

OPDIVO is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

1.10 Urothelial Carcinoma

OPDIVO is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC *[see Clinical Studies (14.10)]*.

OPDIVO, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

OPDIVO is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

1.11 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

- OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).
- OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

1.12 Hepatocellular Carcinoma

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC).
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult patients with unresectable or metastatic HCC who have been previously treated with sorafenib.

1.13 Esophageal Cancer

- OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1) *[see Dosage and Administration (2.1)]*.
- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1) *[see Dosage and Administration (2.1)]*.
- OPDIVO is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

1.14 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (≥1) *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on FDA-approved tests for patient selection is available at:

https://www.fda.gov/CompanionDiagnostics

Non-Small Cell Lung Cancer

- Select patients with metastatic NSCLC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.5)]*.

Esophageal Cancer

- Select patients with unresectable advanced or metastatic ESCC for treatment with OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy based on PD-L1 expression *[see Clinical Studies (14.13)]*.
- Select patients with unresectable advanced or metastatic ESCC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.13)]*.

- An FDA-approved companion diagnostic for the detection of PD-L1 expression in patients with advanced or metastatic ESCC is not available.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- Select patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma for treatment with OPDIVO in combination with fluoropyrimidine-and platinum-containing chemotherapy based on PD-L1 expression *[see Clinical Studies (14.14)]*.

- An FDA-approved companion diagnostic for the detection of PD-L1 expression in patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma is not available.

2.2 Recommended Dosage

The recommended dosages of intravenous OPDIVO as a single agent are presented in Table 1.

Administer OPDIVO as a 30-minute intravenous infusion *[see Dosage and Administration (2.4)]*.

Table 1: Recommended Dosages for Intravenous OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Metastatic non-small cell lung cancer	240 mg every 2 weeks or 480 mg every 4 weeks	Until disease progression or unacceptable toxicity
Advanced renal cell carcinoma		
Classical Hodgkin lymphoma		
Squamous cell carcinoma of the head and neck		
Locally advanced or metastatic urothelial carcinoma		
Esophageal squamous cell carcinoma		
Unresectable or metastatic melanoma	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks	

Table 1: Recommended Dosages for Intravenous OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Adjuvant treatment of melanoma	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks	Until disease recurrence or unacceptable toxicity for up to 1 year
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks	
Adjuvant treatment of urothelial carcinoma (UC)	240 mg every 2 weeks or 480 mg every 4 weeks	Until disease recurrence or unacceptable toxicity for up to 1 year
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following prior treatment for metastatic disease	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks	
Adjuvant treatment of resected esophageal or gastroesophageal junction cancer	240 mg every 2 weeks or 480 mg every 4 weeks	Until disease progression or unacceptable toxicity for a total treatment duration of 1 year

The recommended dosages of OPDIVO in combination with other therapeutic agents are presented in Table 2. Administer OPDIVO on the same day as other therapeutic agents.

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO for the recommended dosage information, as appropriate.

Table 2: Recommended Dosages of Intravenous OPDIVO in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks with ipilimumab 3 mg/kg	In combination with ipilimumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks	
Neoadjuvant treatment of resectable non-small cell lung cancer	360 mg every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles
Neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer	Neoadjuvant: 360 mg every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks	Neoadjuvant treatment in combination with chemotherapy for up to 4 cycles or until disease progression or unacceptable toxicity, followed by adjuvant treatment with OPDIVO as a single agent after surgery for up to 13 cycles (approximately 1 year) or until disease recurrence or unacceptable toxicity
	Adjuvant: 480 mg every 4 weeks	
Metastatic non-small cell lung cancer expressing PD-L1	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
		2 cycles of histology-based platinum-doublet chemotherapy

Table 2: Recommended Dosages of Intravenous OPDIVO in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Malignant pleural mesothelioma	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Advanced renal cell carcinoma	3 mg/kg every 3 weeks with ipilimumab 1 mg/kg	In combination with ipilimumab for 4 doses
	240 mg every 2 weeks or 480 mg every 4 weeks	After completing 4 doses of combination therapy with ipilimumab, administer as single agent until disease progression or unacceptable toxicity
	240 mg every 2 weeks or 480 mg every 4 weeks Administer OPDIVO in combination with cabozantinib 40 mg orally once daily without food	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years
		Cabozantinib: Until disease progression or unacceptable toxicity
First-line unresectable or metastatic urothelial carcinoma	360 mg every 3 weeks Administer OPDIVO in combination with cisplatin and gemcitabine on the same day every 3 weeks	In combination with cisplatin and gemcitabine for up to 6 cycles
	240 mg every 2 weeks or 480 mg every 4 weeks	After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose

Table 2: Recommended Dosages of Intravenous OPDIVO in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 3 weeks with ipilimumab 1 mg/kg	In combination with ipilimumab for a maximum of 4 doses
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 3 weeks with ipilimumab 1 mg/kg	
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity, or up to 2 years
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks	
Hepatocellular carcinoma	1 mg/kg every 3 weeks with ipilimumab 3 mg/kg	In combination with ipilimumab for a maximum of 4 doses
	240 mg every 2 weeks or 480 mg every 4 weeks	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years
Esophageal squamous cell carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks Administer OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years
		Chemotherapy: Until disease progression or unacceptable toxicity
	3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years

Table 2: Recommended Dosages of Intravenous OPDIVO in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Gastric cancer, Gastroesophageal junction cancer, and Esophageal adenocarcinoma	240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	Until disease progression, unacceptable toxicity, or up to 2 years

2.3 Dosage Modifications

No dose reduction for OPDIVO is recommended. In general, withhold OPDIVO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue OPDIVO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for OPDIVO or OPDIVO in combination for adverse reactions that require management different from these general guidelines are summarized in Table 3 and Table 4.

When OPDIVO is administered in combination with ipilimumab, withhold or permanently discontinue both ipilimumab and OPDIVO for an adverse reaction meeting these dose modification guidelines.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[a]
	Grades 3 or 4	Permanently discontinue
Colitis For colitis in patients treated with combination therapy with ipilimumab, see Table 4.	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy with ipilimumab, see Table 4.	AST/ALT increases to >3 and ≤8 times ULN or Total bilirubin increases to >1.5 and ≤3 times ULN.	Withhold[a]
	AST or ALT increases to >8 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Hepatitis with tumor involvement of the liver[b] For liver enzyme elevations in patients treated with combination therapy with ipilimumab, see Table 4.	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold[a]
	AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Endocrinopathies[c]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO based on recommendations for hepatitis with no liver involvement.

[c] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

Table 4: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with Combination Therapy

Treatment	Adverse Reaction	Severity	Dosage Modification
OPDIVO in combination with ipilimumab	Colitis	Grade 2	Withhold[a]
		Grade 3 or 4	Permanently discontinue
	Hepatitis with no tumor involvement of the liver or Hepatitis with tumor involvement of the liver/non-HCC	AST/ALT increases to >3 times ULN and ≤5 times ULN or Total bilirubin increases to ≥1.5 and ≤3 times ULN.	Withhold[a]
		AST or ALT >5 times ULN or Total bilirubin >3 times ULN.	Permanently discontinue
	Hepatitis with tumor involvement of the liver[b]/HCC	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold[a]

Table 4: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with Combination Therapy

Treatment	Adverse Reaction	Severity	Dosage Modification
		AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
OPDIVO in combination with cabozantinib	Liver enzyme elevations	ALT or AST >3 times ULN but ≤10 times ULN with concurrent total bilirubin <2 times ULN	Withhold[c] both OPDIVO and cabozantinib until adverse reactions recover[d] to Grades 0-1
		ALT or AST >10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN	Permanently discontinue[c] both OPDIVO and cabozantinib

[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO in combination with ipilimumab based on recommendations for hepatitis with no liver involvement.

[c] Consider corticosteroid therapy for hepatic adverse reactions if OPDIVO is withheld or discontinued when administered in combination with cabozantinib.

[d] After recovery, rechallenge with one or both of OPDIVO and cabozantinib may be considered. If rechallenging with cabozantinib with or without OPDIVO, refer to cabozantinib Prescribing Information.

2.4 Preparation and Administration

Visually inspect for particulate matter and discoloration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard if cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake.

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
  - For adult and pediatric patients with body weight 40 kg or greater, **do not exceed a total volume of infusion of 160 mL.**
  - For adult and pediatric patients with body weight less than 40 kg, do not exceed a total volume of infusion of 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.

- Discard partially used vials or empty vials of OPDIVO.
- The product does not contain a preservative.
- After preparation, store the diluted solution either:
  - at room temperature at 20°C to 25°C (68°F to 77°F) and room light for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
  - under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light for no more than 7 days from the time of preparation to end of infusion. Discard diluted solution if not used within 7 days from the time of preparation.
- Do not freeze.

Administration

- Administer the infusion, after dilution, over 30 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Administer OPDIVO in combination with other therapeutic agents as follows:

Combination Therapy	
Ipilimumab	Administer OPDIVO first, followed by the other therapeutic agent(s).
Platinum-Doublet Chemotherapy	
Ipilimumab and Platinum-Doublet Chemotherapy	
Fluoropyrimidine- and Platinum-Containing Chemotherapy	

- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

OPDIVO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse

reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.3)]*. In general, if OPDIVO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

OPDIVO as a Single Agent

Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO in 1.1% and withholding of OPDIVO in 0.8% of patients.

Systemic corticosteroids were required in 100% (61/61) of patients with pneumonitis. Pneumonitis resolved in 84% of the 61 patients. Of the 15 patients in whom OPDIVO was withheld for pneumonitis, 14 reinitiated OPDIVO after symptom improvement; of these, 4 (29%) had recurrence of pneumonitis.

OPDIVO with Ipilimumab

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg

every 6 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 5% of patients and withholding of OPDIVO with ipilimumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after reinitiation of OPDIVO with ipilimumab.

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

OPDIVO as a Single Agent

Immune-mediated colitis occurred in 2.9% (58/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (1.7%) and Grade 2 (1%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.9% of patients.

Systemic corticosteroids were required in 100% (58/58) of patients with colitis. Four patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 86% of the 58 patients. Of the 18 patients in whom OPDIVO was withheld for colitis, 16 reinitiated OPDIVO after symptom improvement; of these, 12 (75%) had recurrence of colitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated colitis occurred in 25% (115/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.4%), Grade 3 (14%), and Grade 2 (8%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 14% and withholding of OPDIVO with ipilimumab in 4.4% of patients.

Systemic corticosteroids were required in 100% (115/115) of patients with colitis. Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 93% of the 115 patients. Of the 20 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 9 (56%) had recurrence of colitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated colitis occurred in 9% (60/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (4.4%) and Grade 2 (3.7%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.2% and withholding of OPDIVO with ipilimumab in 2.7% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (60/60) of patients with colitis. Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 10 (63%) had recurrence of colitis.

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

OPDIVO as a Single Agent

Immune-mediated hepatitis occurred in 1.8% (35/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.6% of patients.

Systemic corticosteroids were required in 100% (35/35) of patients with hepatitis. Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 35 patients. Of the 12 patients in whom OPDIVO was withheld for hepatitis, 11 reinitiated OPDIVO after symptom improvement; of these, 9 (82%) had recurrence of hepatitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated hepatitis occurred in 15% (70/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 8% or withholding of OPDIVO with ipilimumab in 3.5% of patients.

Systemic corticosteroids were required in 100% (70/70) of patients with hepatitis. Approximately 9% of patients with immune-mediated hepatitis required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 70 patients. Of the 16 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 8 (57%) had recurrence of hepatitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated hepatitis occurred in 7% (48/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.6% and withholding of OPDIVO with ipilimumab in 2.6% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (48/48) of patients with hepatitis. Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 10 (71%) had recurrence of hepatitis.

OPDIVO with Cabozantinib

OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt OPDIVO and cabozantinib and consider administering corticosteroids *[see Dosage and Administration (2.3)]*.

With the combination of OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients *[see Adverse Reactions (6.1)]*. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either OPDIVO (n=11) or cabozantinib (n=9) administered as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving OPDIVO, 2 patients receiving cabozantinib, and 7 patients receiving both OPDIVO and cabozantinib.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

OPDIVO can cause primary or secondary adrenal insufficiency. For grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

Adrenal insufficiency occurred in 1% (20/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.4% of patients.

Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 90% (18/20) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 35% of the 20 patients. Of the 8 patients in whom OPDIVO was withheld for adrenal insufficiency, 4 reinitiated OPDIVO after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Adrenal insufficiency occurred in 8% (35/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 2% of patients.

Approximately 71% (25/35) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 37% of the 35 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for adrenal

insufficiency, 7 reinitiated treatment after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Adrenal insufficiency occurred in 7% (48/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 94% (45/48) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 11 reinitiated treatment after symptom improvement; of these, all received hormone replacement therapy and 2 (18%) had recurrence of adrenal insufficiency.

OPDIVO with Cabozantinib

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received OPDIVO with cabozantinib, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO and cabozantinib in 0.9% and withholding of OPDIVO and cabozantinib in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom OPDIVO with cabozantinib was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

Hypophysitis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO in <0.1% and withholding of OPDIVO in 0.2% of patients.

Approximately 67% (8/12) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 42% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for hypophysitis, 2 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hypophysitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hypophysitis occurred in 9% (42/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (2.4%) and Grade 2 (6%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 4.2% of patients.

Approximately 86% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 88% (37/42) of patients with hypophysitis. Hypophysitis resolved in 38% of the 42 patients. Of the 19 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 9 reinitiated treatment after symptom improvement; of these, 1 (11%) had recurrence of hypophysitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hypophysitis occurred in 4.4% (29/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 72% (21/29) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 11 reinitiated treatment after symptom improvement; of these, 2 (18%) had recurrence of hypophysitis.

Thyroid Disorders

OPDIVO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.3)]*.

Thyroiditis

OPDIVO as a Single Agent

Thyroiditis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 2 (0.2%) adverse reactions. Thyroiditis led to permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.2% of patients.

Systemic corticosteroids were required in 17% (2/12) of patients with thyroiditis. Thyroiditis resolved in 58% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for thyroiditis, 1 reinitiated OPDIVO after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism

OPDIVO as a Single Agent

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (<0.1%) and Grade 2 (1.2%) adverse reactions. Hyperthyroidism led to the

permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.4% of patients.

Approximately 19% of patients with hyperthyroidism received methimazole, 7% received carbimazole, and 4% received propylthiouracil. Systemic corticosteroids were required in 9% (5/54) of patients. Hyperthyroidism resolved in 76% of the 54 patients. Of the 7 patients in whom OPDIVO was withheld for hyperthyroidism, 4 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hyperthyroidism.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hyperthyroidism occurred in 9% (42/456) of patients with melanoma or HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.9%) and Grade 2 (4.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.4% of patients.

Approximately 26% of patients with hyperthyroidism received methimazole and 21% received carbimazole. Systemic corticosteroids were required in 17% (7/42) of patients. Hyperthyroidism resolved in 91% of the 42 patients. Of the 11 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 8 reinitiated treatment after symptom improvement; of these, 1 (13%) had recurrence of hyperthyroidism.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hyperthyroidism occurred in 12% (80/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (4.5%) adverse reactions. Hyperthyroidism led to permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.3% of patients with RCC or CRC.

Of the 80 patients with RCC or CRC who developed hyperthyroidism, approximately 16% received methimazole and 3% received carbimazole. Systemic corticosteroids were required in 20% (16/80) of patients with hyperthyroidism. Hyperthyroidism resolved in 85% of the 80 patients. Of the 15 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 11 reinitiated treatment after symptom improvement; of these, 3 (27%) had recurrence of hyperthyroidism.

Hypothyroidism

OPDIVO as a Single Agent

Hypothyroidism occurred in 8% (163/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (4.8%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.5% of patients.

Approximately 79% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 3.1% (5/163) of patients with hypothyroidism. Hypothyroidism resolved in 35% of the 163 patients. Of the 9 patients in whom OPDIVO was withheld for

hypothyroidism, 3 reinitiated OPDIVO after symptom improvement; of these, 1 (33%) had recurrence of hypothyroidism.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hypothyroidism occurred in 20% (91/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.4%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 0.9% of patients.

Approximately 89% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 2.2% (2/91) of patients with hypothyroidism. Hypothyroidism resolved in 41% of the 91 patients. Of the 4 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement; of these, none had recurrence of hypothyroidism.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hypothyroidism occurred in 18% (122/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to permanent discontinuation of OPDIVO with ipilimumab in 0.2% and withholding of OPDIVO with ipilimumab in 1.4% of patients with RCC or CRC.

Of the 122 patients with RCC or CRC who developed hypothyroidism, approximately 82% received levothyroxine. Systemic corticosteroids were required in 7% (9/122) of patients with hypothyroidism. Hypothyroidism resolved in 27% of the 122 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 5 reinitiated treatment after symptom improvement; of these, 1 (20%) had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

Diabetes occurred in 0.9% (17/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.3%) adverse reactions, and two cases of diabetic ketoacidosis. Diabetes led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.1% of patients.

No patients (0/17) with diabetes required systemic corticosteroids. Diabetes resolved in 29% of the 17 patients. Of the 2 patients in whom OPDIVO was withheld for diabetes, both reinitiated OPDIVO after symptom improvement; of these, neither had recurrence of diabetes.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology.

OPDIVO as a Single Agent

Immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.4% of patients.

Systemic corticosteroids were required in 100% (23/23) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 78% of the 23 patients. Of the 7 patients in whom OPDIVO was withheld for nephritis or renal dysfunction, 7 reinitiated OPDIVO after symptom improvement; of these, 1 (14%) had recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

Immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.5% of patients.

Systemic corticosteroids were required in 100% (171/171) of patients with immune-mediated rash. Rash resolved in 72% of the 171 patients. Of the 10 patients in whom OPDIVO was withheld for immune-mediated rash, 9 reinitiated OPDIVO after symptom improvement; of these, 3 (33%) had recurrence of immune-mediated rash.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated rash occurred in 28% (127/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (4.8%) and Grade 2 (10%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 3.9% of patients.

Systemic corticosteroids were required in 100% (127/127) of patients with immune-mediated rash. Rash resolved in 84% of the 127 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 15 reinitiated treatment after symptom improvement; of these, 8 (53%) had recurrence of immune-mediated rash.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated rash occurred in 16% (108/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (3.5%) and Grade 2 (4.2%) adverse reactions. Immune-mediated rash

led to permanent discontinuation of OPDIVO with ipilimumab in 0.5% of patients and withholding of OPDIVO with ipilimumab in 2.0% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (108/108) of patients with immune-mediated rash. Rash resolved in 75% of the 108 patients. Of the 13 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 11 reinitiated treatment after symptom improvement; of these, 5 (46%) had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO or OPDIVO in combination with ipilimumab, or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatic

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection

5.2 Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions, which have been reported in <1% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients.

In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received OPDIVO as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation, or withholding of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Infusion-related reactions occurred in 2.5% (10/407) of patients with melanoma and in 8% (4/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Infusion-related reactions occurred in 5.1% (28/547) of patients with RCC and 4.2% (5/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, respectively. Infusion-related reactions occurred in 12% (37/300) of patients with malignant pleural mesothelioma who received OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks.

5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause) *[see Adverse Reactions (6.1)]*. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Increased Mortality in Patients with Multiple Myeloma when OPDIVO Is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no

PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142; OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in patients enrolled in CHECKMATE-227 (n=576) or CHECKMATE-743 (n=300); OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361); and OPDIVO 240 mg with cabozantinib 40 mg in patients enrolled in CHECKMATE-9ER (n=320).

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The safety of OPDIVO was evaluated in CHECKMATE-037, a randomized, open-label trial in 370 patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102): dacarbazine 1000 mg/m^2 intravenously every 3 weeks or carboplatin AUC 6 mg/mL/min and paclitaxel 175 mg/m^2 intravenously every 3 weeks. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) in OPDIVO-treated patients and was

2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received OPDIVO for >6 months and 3% of patients received OPDIVO for >1 year.

The population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% White, baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated lactate dehydrogenase (LDH) at baseline (51% vs. 38%).

Serious adverse reactions occurred in 41% of patients receiving OPDIVO. OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a dose interruption for an adverse reaction. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reaction (reported in ≥20% of patients) was rash.

Tables 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-037.

Table 5: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, Thoracic and Mediastinal				
Cough	17	0	6	0
Infections				
Upper respiratory tract infection[b]	11	0	2	0
General				
Peripheral edema	10	0	5	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, and acneiform dermatitis.

[b] Includes rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

Skin and Subcutaneous Tissue Disorders: exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

Table 6: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037

Laboratory Abnormality	OPDIVO		Chemotherapy	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased AST	28	2.4	12	1
Hyponatremia	25	5	18	1.1
Increased alkaline phosphatase	22	2.4	13	1.1
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2	6	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 252 to 256 patients) and chemotherapy group (range: 94 to 96 patients).

Previously Untreated Metastatic Melanoma

CHECKMATE-066

The safety of OPDIVO was also evaluated in CHECKMATE-066, a randomized, double-blind, active-controlled trial in 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n=205). The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for >6 months and 12% of patients received OPDIVO for >1 year.

The trial population characteristics in the OPDIVO group and dacarbazine group: 59% male, median age 65 years, 99.5% White, 61% with M1c stage disease, 74% with cutaneous melanoma,

11% with mucosal melanoma, 4% with brain metastasis, and 37% with elevated LDH at baseline. There were more patients in the OPDIVO group with ECOG performance status 0 (71% vs. 59%).

Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Adverse reactions led to permanent discontinuation of OPDIVO in 7% of patients and dose interruption in 26% of patients; no single type of adverse reaction accounted for the majority of OPDIVO discontinuations. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were increased gamma-glutamyl transferase (3.9%) and diarrhea (3.4%). The most common adverse reactions (reported in ≥20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

Tables 7 and 8 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-066.

Table 7: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066

Adverse Reaction	OPDIVO (n=206)		Dacarbazine (n=205)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue	49	1.9	39	3.4
Edema[a]	12	1.5	4.9	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	32	2.9	25	2.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.5	12	0
Pruritus	23	0.5	12	0
Vitiligo	11	0	0.5	0
Erythema	10	0	2.9	0
Infections				
Upper respiratory tract infection[d]	17	0	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema.

[b] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, pain in jaw, and spinal pain.

[c] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, dermatitis, allergic dermatitis, exfoliative dermatitis, acneiform dermatitis, drug eruption, and skin reaction.

[d] Includes rhinitis, viral rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

Nervous System Disorders: peripheral neuropathy

Table 8: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066

Laboratory Abnormality	OPDIVO		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	25	3	19	0.5
Increased AST	24	3.6	19	0.5
Increased alkaline phosphatase	21	2.6	14	1.6
Increased bilirubin	13	3.1	6	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 194 to 197 patients) and dacarbazine group (range: 186 to 193 patients).

CHECKMATE-067

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in CHECKMATE-067, a randomized (1:1:1), double-blind trial in 937 patients with previously untreated, unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

Patients were randomized to receive:

- OPDIVO 1 mg/kg over 60 minutes with ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO and ipilimumab arm; n=313), or
- OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO arm; n=313), or
- Ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for up to 4 doses (ipilimumab arm; n=311).

The median duration of exposure to OPDIVO was 2.8 months (range: 1 day to 36.4 months) for the OPDIVO and ipilimumab arm and 6.6 months (range: 1 day to 36.0 months) for the OPDIVO arm. In the OPDIVO and ipilimumab arm, 39% were exposed to OPDIVO for ≥6 months and 30% exposed for >1 year. In the OPDIVO arm, 53% were exposed for ≥6 months and 40% for >1 year.

The population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with American Joint Committee on Cancer (AJCC) Stage IV disease, 58% with M1c stage disease; 36% with elevated LDH at baseline, 4% with a history of brain metastasis, and 22% had received adjuvant therapy.

Serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO and ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO and ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO and ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were colitis (10% and 0.6%), diarrhea (8% and 2.2%), increased ALT (4.8% and 1%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%).

The most common (≥20%) adverse reactions in the OPDIVO and ipilimumab arm were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases. The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue, rash, musculoskeletal pain, diarrhea, nausea, cough, pruritus, upper respiratory tract infection, decreased appetite, headache, constipation, arthralgia, and vomiting.

Tables 9 and 10 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

Table 9: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO and Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Adverse Reaction	OPDIVO and Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General						
Fatigue[a]	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1	17	1.6

Table 9: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO and Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Adverse Reaction	OPDIVO and Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue						
Rash[b]	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[c]	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1	16	0.3
Metabolism and Nutrition						
Decreased appetite	29	1.9	22	0	24	1.3
Respiratory, Thoracic and Mediastinal						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections						
Upper respiratory tract infection[d]	23	0	22	0.3	17	0
Endocrine						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular						
Hypertension[e]	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia and fatigue.

[b] Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, and pruritic rash.

[c] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

[d] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

[e] Includes hypertension and blood pressure increased.

Clinically important adverse reactions in <10% of patients who received OPDIVO with ipilimumab or OPDIVO as a single agent were:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

Musculoskeletal and Connective Tissue Disorders: myopathy, Sjogren's syndrome, spondyloarthropathy, myositis (including polymyositis)

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 10: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients Treated with OPDIVO with Ipilimumab or Single-Agent OPDIVO and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Laboratory Abnormality	OPDIVO and Ipilimumab		OPDIVO		Ipilimumab	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry						
Increased ALT	55	16	25	3	29	2.7
Hyperglycemia	53	5.3	46	7	26	0
Increased AST	52	13	29	3.7	29	1.7
Hyponatremia	45	10	22	3.3	26	7
Increased lipase	43	22	32	12	24	7
Increased alkaline phosphatase	41	6	27	2	23	2
Hypocalcemia	31	1.1	15	0.7	20	0.7
Increased amylase	27	10	19	2.7	15	1.6
Increased creatinine	26	2.7	19	0.7	17	1.3
Hematology						
Anemia	52	2.7	41	2.6	41	6
Lymphopenia	39	5	41	4.9	29	4

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab (range: 75 to 297); OPDIVO (range: 81 to 306); ipilimumab (range: 61 to 301).

Adjuvant Treatment of Melanoma

CHECKMATE-76K

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-76K, a randomized (2:1), double-blind trial in 788 patients with completely resected Stage IIB/C melanoma who received OPDIVO 480 mg by intravenous infusion over 30 minutes every 4 weeks (n=524) or placebo by intravenous infusion over 30 minutes every 4 weeks (n=264) for up to 1 year *[see Clinical Studies (14.2)]*. The median duration of exposure was 11 months in patients treated with OPDIVO and 11 months in patients treated with placebo.

Serious adverse reactions occurred in 18% of patients treated with OPDIVO. A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). Permanent discontinuation of OPDIVO due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of OPDIVO in >1% of patients included diarrhea (1.1%), arthralgia (1.7%), and rash (1.7%).

Dosage interruptions of OPDIVO due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dosage interruption in >1% of patients included COVID-19 infection, infusion related reaction, diarrhea, arthralgia, and increased ALT.

The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, rash, diarrhea, and pruritus.

Tables 11 and 12 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-76K.

Table 11: Adverse Reactions Occurring in ≥10% of Patients Treated with OPDIVO - CHECKMATE-76K

Adverse Reaction	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	36	0.4	34	0.4
Musculoskeletal and connective tissue				
Musculoskeletal pain[b]	30	0.4	26	0.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.1	15	0.4
Pruritus	20	0.2	11	0
Gastrointestinal				
Diarrhea[d]	23	1.3	16	0
Nausea	14	0	11	0
Endocrine				

Table 11: Adverse Reactions Occurring in ≥10% of Patients Treated with OPDIVO - CHECKMATE-76K

Adverse Reaction	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hypothyroidism[e]	14	0	2.3	0
Nervous system				
Headache[f]	12	0.2	14	0.8

Toxicity was graded per NCI CTCAE v5.

[a] Includes asthenia.

[b] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, spinal pain, pain in extremity.

[c] Includes dermatitis, dermatitis acneiform, dyshidrotic eczema, eczema, eczema asteatotic, eyelid rash, genital rash, pemphigoid, penile rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, toxic skin eruption.

[d] Includes autoimmune colitis, colitis, diarrhea, enteritis, enterocolitis.

[e] Includes autoimmune hypothyroidism, blood thyroid stimulating hormone increased.

[f] Includes cluster headache, migraine.

Table 12: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-76K

Laboratory Abnormality	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	19	0	14	0
Lymphopenia	17	1.1	17	1.7
Neutropenia	10	0	10	0.4
Chemistry				
AST increased	25	2.2	16	0.4
Lipase increased	22	2.9	21	2.3
ALT increased	20	2.1	15	0.4
Amylase increased	17	0.4	9	0
Creatinine increased	15	0.4	13	0
Sodium decreased	13	0.6	11	0.4
Potassium increased	13	1	15	1.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 262 to 513 patients) and placebo group (range: 138 to 261 patients).

CHECKMATE-238

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg by intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year (n=453) *[see Clinical Studies (14.2)]*. The median duration of exposure was 11.5 months in OPDIVO-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received OPDIVO for >6 months.

Serious adverse reactions occurred in 18% of OPDIVO-treated patients. Study therapy was discontinued for adverse reactions in 9% of OPDIVO-treated patients and 42% of ipilimumab-treated patients. Twenty-eight percent of OPDIVO-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions (at least 20%) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

Tables 13 and 14 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

Table 13: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Adverse Reaction	OPDIVO (n=452)		Ipilimumab 10 mg/kg (n=453)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	57	0.9	55	2.4
Gastrointestinal				
Diarrhea	37	2.4	55	11
Nausea	23	0.2	28	0
Abdominal pain[b]	21	0.2	23	0.9
Constipation	10	0	9	0
Skin and Subcutaneous Tissue				
Rash[c]	35	1.1	47	5.3
Pruritus	28	0	37	1.1
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	32	0.4	27	0.4

Table 13: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Adverse Reaction	OPDIVO (n=452)		Ipilimumab 10 mg/kg (n=453)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Arthralgia	19	0.4	13	0.4
Nervous System				
Headache	23	0.4	31	2.0
Dizziness[e]	11	0	8	0
Infections				
Upper respiratory tract infection[f]	22	0	15	0.2
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	19	0	19	0
Dyspnea/exertional dyspnea	10	0.4	10	0.2
Endocrine				
Hypothyroidism[g]	12	0.2	7.5	0.4

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.

[c] Includes dermatitis described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.

[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.

[e] Includes postural dizziness and vertigo.

[f] Includes upper respiratory tract infection including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.

[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

Table 14: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Laboratory Abnormality	OPDIVO		Ipilimumab 10 mg/kg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	27	0.4	12	0.9
Anemia	26	0	34	0.5
Leukopenia	14	0	2.7	0.2
Neutropenia	13	0	6	0.5
Chemistry				
Increased Lipase	25	7	23	9

Table 14: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Laboratory Abnormality	OPDIVO		Ipilimumab 10 mg/kg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	25	1.8	40	12
Increased AST	24	1.3	33	9
Increased Amylase	17	3.3	13	3.1
Hyponatremia	16	1.1	22	3.2
Hyperkalemia	12	0.2	9	0.5
Increased Creatinine	12	0	13	0
Hypocalcemia	10	0.7	16	0.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 400 to 447 patients) and ipilimumab 10 mg/kg group (range: 392 to 443 patients).

Neoadjuvant Treatment of Resectable (Tumors ≥4 cm or Node Positive) Non-Small Cell Lung Cancer

The safety of OPDIVO in combination with platinum-doublet chemotherapy was evaluated in CHECKMATE-816, a randomized, open-label, multicenter trial in patients with resectable NSCLC *[see Clinical Studies (14.3)]*. Patients received either OPDIVO 360 mg administered in combination with platinum-doublet chemotherapy administered every 3 weeks for 3 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 3 cycles.

The median age of patients who received OPDIVO in combination with platinum-doublet chemotherapy or platinum-doublet chemotherapy was 65 years (range: 34 – 84); 72% male; 47% White, 50% Asian, and 2% Black/African American.

Serious adverse reactions occurred in 30% of patients who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy.

Study therapy with OPDIVO in combination with platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 10% of patients and 30% had at least one treatment withheld for an adverse reaction. The most common adverse reactions (≥1%) resulting in permanent discontinuation of OPDIVO in combination with platinum-doublet chemotherapy were anaphylactic reaction (1.7%), acute kidney injury (1.1%), rash (1.1%), and fatigue (1.1%).

The most common (>20%) adverse reactions were nausea, constipation, fatigue, decreased appetite, and rash. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were neutropenia, hyperglycemia, leukopenia, lymphopenia, increased amylase, anemia, thrombocytopenia, and hyponatremia.

Tables 15 and 16 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-816.

Table 15: Adverse Reactions in >10% of Patients with Early-Stage NSCLC Receiving Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy in CHECKMATE-816

Adverse Reaction	OPDIVO and Platinum-Doublet Chemotherapy (n=176)		Platinum-Doublet Chemotherapy (n=176)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				
Nausea	38	0.6	45	1.1
Constipation	34	0	32	1.1
Vomiting	11	1.1	13	0.6
General				
Fatigue[a]	26	2.3	23	1.1
Malaise	15	0.6	14	0.6
Metabolism and Nutrition				
Decreased appetite	20	1.1	23	2.3
Skin and Subcutaneous Tissue				
Rash[b]	20	2.3	7	0
Alopecia	11	0	15	0
Nervous System				
Peripheral neuropathy[c]	13	0	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia.

[b] Includes rash, dermatitis, acneiform dermatitis, atopic dermatitis, bullous dermatitis, drug eruption, maculopapular rash, and pruritic rash.

[c] Includes peripheral neuropathy, dysesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensory neuropathy.

Table 16: Select Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients with Early-Stage NSCLC Receiving Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy in CHECKMATE-816

Laboratory Abnormality	OPDIVO and Platinum-Doublet Chemotherapy[a]		Platinum-Doublet Chemotherapy[a]	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Anemia	63	3.5	70	6
Neutropenia	58	22	58	27
Leukopenia	53	5	51	11
Lymphopenia	38	4.7	31	1.8
Thrombocytopenia	24	2.9	22	3
Chemistry				
Hyperglycemia	37	6	35	2.9
Hypomagnesemia	25	1.2	29	1.2
Hyponatremia	25	2.4	28	1.8
Increased amylase	23	3.6	13	1.8
Increased ALT	23	0	20	1.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and platinum-doublet chemotherapy group (range: 73 to 171 patients) and platinum-doublet chemotherapy group (range: 68 to 171 patients).

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

The safety of OPDIVO in combination with neoadjuvant platinum-doublet chemotherapy followed by surgery and continued adjuvant treatment with OPDIVO as a single agent after surgery was evaluated in CHECKMATE-77T, a randomized, double-blind, multicenter trial in patients with previously untreated resectable Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2) NSCLC (per the AJCC Cancer Staging Manual 8th Edition) *[see Clinical Studies (14.4)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. The median duration of exposure to OPDIVO was 10.3 months (range: 1 day to 22.3 months).

The study population characteristics were: median age 66 years (range: 35 - 86); 71% male; 72% White, 25% Asian, 1.7% Black/African American, and 1.5% other race; and 6% Hispanic or Latino.

Adverse reactions occurring in patients with resectable NSCLC receiving OPDIVO in combination with platinum-doublet chemotherapy, given as neoadjuvant treatment and followed as a single agent adjuvant treatment after surgery, were generally similar to those occurring in patients in other clinical trials across tumor types receiving OPDIVO in combination with chemotherapy.

Neoadjuvant Phase of CHECKMATE-77T

A total of 228 patients received at least 1 dose of OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment and 230 patients received at least 1 dose of placebo in combination with platinum-doublet chemotherapy as neoadjuvant treatment.

Serious adverse reactions occurred in 21% of patients who received OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions was pneumonia. Fatal adverse reactions occurred in 2.2% of patients, due to cerebrovascular accident, COVID-19 infection, hemoptysis, pneumonia, and pneumonitis (0.4% each).

Permanent discontinuation of any study drug due to an adverse reaction occurred in 13% of patients who received OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reaction that led to permanent discontinuation of any study drug was peripheral sensory neuropathy (2.2%).

Of the 228 OPDIVO-treated patients and 230 placebo-treated patients who received neoadjuvant treatment, 5.3% (n=12) and 3.5% (n=8), respectively, did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery in OPDIVO-treated patients were cerebrovascular accident, pneumonia, and colitis/diarrhea (2 patients each) and acute coronary syndrome, myocarditis, hemoptysis, pneumonitis, COVID-19, and myositis (1 patient each).

Of the 178 OPDIVO-treated patients who received surgery, 4.5% (n=8) experienced delay of surgery (surgery more than 6 weeks from last neoadjuvant treatment) due to adverse reactions. Of the 178 placebo-treated patients who received surgery, 3.9% (n=7) experienced delay of surgery due to adverse reactions.

Of the 178 OPDIVO-treated patients who received surgery, 7% (n=13) did not receive adjuvant treatment due to adverse reactions. Of the 178 placebo-treated patients who received surgery, 2.8% (n=5) did not receive adjuvant treatment due to adverse reactions.

Adjuvant Phase of CHECKMATE-77T

A total of 142 patients in the OPDIVO arm and 152 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent OPDIVO as adjuvant treatment, 22% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonitis/ILD (2.8%). One fatal adverse reaction due to COVID-19 occurred. Permanent discontinuation of adjuvant OPDIVO due to an adverse reaction occurred in 14% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant OPDIVO were pneumonitis (4.2%) and diarrhea (1.4%).

Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.5)]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received OPDIVO 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received OPDIVO and ipilimumab for >6 months and 23% of patients received OPDIVO and ipilimumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Serious adverse reactions occurred in 58% of patients. OPDIVO and ipilimumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus.

Tables 17 and 18 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 17: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5

Table 17: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1	18	2.3
Abdominal pain[g]	10	0.2	9	0.7
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.

[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.

[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.

[d] Includes pruritus and pruritus generalized.

[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.

[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.

[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.

[h] Includes dyspnea and dyspnea exertional.

[i] Includes cough and productive cough.

[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.

[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.

[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.

[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were:

Skin and Subcutaneous Tissue: urticaria, alopecia, erythema multiforme, vitiligo

Gastrointestinal: stomatitis, pancreatitis, gastritis

Musculoskeletal and Connective Tissue: arthritis, polymyalgia rheumatica, rhabdomyolysis

Nervous System: peripheral neuropathy, autoimmune encephalitis

Blood and Lymphatic System: eosinophilia

Eye Disorders: blurred vision, uveitis

Cardiac: atrial fibrillation, myocarditis

Table 18: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227

Laboratory Abnormality	OPDIVO and Ipilimumab		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
Hyponatremia	41	12	26	4.9

Table 18: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227

Laboratory Abnormality	OPDIVO and Ipilimumab		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.5)]*. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 19 and 20 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 19: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia.

[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis.

[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis.

[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain.

[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blennorrhagica, palmar-plantar erythrodysesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria.

[f] Includes pruritus and generalized pruritus.

[g] Includes cough, productive cough, and upper-airway cough syndrome.

[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea.

[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine.

[j] Includes dizziness, vertigo and positional vertigo.

Table 20: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6

Table 20: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Second-line Treatment of Metastatic NSCLC

The safety of OPDIVO was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.5)]*. These trials excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m^2 intravenously every 3 weeks. The median duration of therapy in OPDIVO-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for >6 months and 20% of patients received OPDIVO for >1 year.

Across both trials, the median age of OPDIVO-treated patients was 61 years (range: 37 to 85); 38% were ≥65 years of age, 61% were male, and 91% were White. Ten percent of patients had brain metastases and ECOG performance status was 0 (26%) or 1 (74%).

In CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. Across both trials, the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Tables 21 and 22 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

Table 21: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic and Mediastinal				
Cough	31	0.7	24	0
Metabolism and Nutrition				
Decreased appetite	28	1.4	23	1.5
Skin and Subcutaneous Tissue				
Pruritus	10	0.2	2	0

Toxicity was graded per NCI CTCAE v4.

Other clinically important adverse reactions observed in OPDIVO-treated patients and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (48% all Grades, 5% Grade 3-4), musculoskeletal pain (33% all Grades), pleural effusion (4.5% all Grades), pulmonary embolism (3.3% all Grades).

Table 22: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057

Laboratory Abnormality	OPDIVO		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Hyponatremia	35	7	34	4.9
Increased AST	27	1.9	13	0.8
Increased alkaline phosphatase	26	0.7	18	0.8
Increased ALT	22	1.7	17	0.5
Increased creatinine	18	0	12	0.5
Increased TSH[b]	14	N/A	6	N/A

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 405 to 417 patients) and docetaxel group (range: 372 to 390 patients), except for TSH: OPDIVO group n=314 and docetaxel group n=297.

[b] Not graded per NCI CTCAE v4.

Malignant Pleural Mesothelioma

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-743, a randomized, open-label trial in patients with previously untreated unresectable malignant pleural mesothelioma *[see Clinical Studies (14.6)]*. Patients received either OPDIVO 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years; or platinum-doublet chemotherapy for up to 6 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 5.6 months (range: 0 to 26.2 months); 48% of patients received OPDIVO and ipilimumab for >6 months and 24% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 54% of patients who were treated with OPDIVO in combination with ipilimumab. The most frequent (≥2%) serious adverse reactions were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis and encephalitis.

Both OPDIVO and ipilimumab were permanently discontinued due to adverse reactions in 23% of patients and 52% had at least one dose withheld due to an adverse reaction.

The most common (≥20%) adverse reactions were fatigue, musculoskeletal pain, rash, diarrhea, dyspnea, nausea, decreased appetite, cough, and pruritus.

Tables 23 and 24 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-743.

Table 23: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-743

Adverse Reaction	OPDIVO and Ipilimumab (n=300)		Chemotherapy (n=284)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	43	4.3	45	6
Pyrexia[b]	18	1.3	4.6	0.7
Edema[c]	17	0	8	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	38	3.3	17	1.1
Arthralgia	13	1	1.1	0
Skin and Subcutaneous Tissue				
Rash[e]	34	2.7	11	0.4
Pruritus[f]	21	1	1.4	0

Table 23: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-743

Adverse Reaction	OPDIVO and Ipilimumab (n=300)		Chemotherapy (n=284)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea[g]	32	6	12	1.1
Nausea	24	0.7	43	2.5
Constipation	19	0.3	30	0.7
Abdominal pain[h]	15	1	10	0.7
Vomiting	14	0	18	2.1
Respiratory, Thoracic, and Mediastinal				
Dyspnea[i]	27	2.3	16	3.2
Cough[j]	23	0.7	9	0
Metabolism and Nutrition				
Decreased appetite	24	1	25	1.4
Endocrine				
Hypothyroidism[k]	15	0	1.4	0
Infections and Infestations				
Upper respiratory tract infection[l]	12	0.3	7	0
Pneumonia[m]	10	4	4.2	2.1

[a] Includes fatigue and asthenia.

[b] Includes pyrexia and tumor-associated fever.

[c] Includes edema, generalized edema, peripheral edema, and peripheral swelling.

[d] Includes musculoskeletal pain, back pain, bone pain, flank pain, involuntary muscle contractions, muscle spasms, muscle twitching, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, polymyalgia rheumatica, and spinal pain.

[e] Includes rash, acne, acneiform dermatitis, allergic dermatitis, atopic dermatitis, autoimmune dermatitis, bullous dermatitis, contact dermatitis, dermatitis, drug eruption, dyshidrotic eczema, eczema, erythematous rash, exfoliative rash, generalized exfoliative dermatitis, generalized rash, granulomatous dermatitis, keratoderma blennorrhagica, macular rash, maculopapular rash, morbilliform rash, nodular rash, papular rash, psoriasiform dermatitis, pruritic rash, pustular rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, toxic skin eruption, and urticaria.

[f] Includes pruritus, allergic pruritus, and generalized pruritus.

[g] Includes diarrhea, colitis, enteritis, infectious enteritis, enterocolitis, infectious enterocolitis, microscopic colitis, ulcerative colitis, and viral enterocolitis.

[h] Includes abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain, lower abdominal pain, and upper abdominal pain.

[i] Includes dyspnea, dyspnea at rest, and exertional dyspnea.

[j] Includes cough, productive cough, and upper-airway cough syndrome.

[k] Includes hypothyroidism, autoimmune thyroiditis, decreased free tri-iodothyronine, increased blood thyroid stimulating hormone, primary hypothyroidism, thyroiditis, and autoimmune hypothyroidism.

[l] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

[m] Includes pneumonia, lower respiratory tract infection, lung infection, aspiration pneumonia, and Pneumocystis jirovecii pneumonia.

Table 24: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-743

Laboratory Abnormality	OPDIVO and Ipilimumab		Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	53	3.7	34	1.1
Increased AST	38	7	17	0
Increased ALT	37	7	15	0.4
Increased lipase	34	13	9	0.8
Hyponatremia	32	8	21	2.9
Increased alkaline phosphatase	31	3.1	12	0
Hyperkalemia	30	4.1	16	0.7
Hypocalcemia	28	0	16	0
Increased amylase	26	5	13	0.9
Increased creatinine	20	0.3	20	0.4
Hematology				
Lymphopenia	43	8	57	14
Anemia	43	2.4	75	15

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 109 to 297 patients) and chemotherapy group (range: 90 to 276 patients).

Advanced Renal Cell Carcinoma

First-line Renal Cell Carcinoma

CHECKMATE-214

The safety of OPDIVO with ipilimumab was evaluated in CHECKMATE-214, a randomized open-label trial in 1082 patients with previously untreated advanced RCC received OPDIVO 3 mg/kg over 60 minutes with ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (n=547) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=535) *[see Clinical Studies (14.7)]*. The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in OPDIVO and ipilimumab-treated patients and 7.8 months (range: 1 day to 20.2+ months) in

sunitinib-treated patients. In this trial, 57% of patients in the OPDIVO and ipilimumab arm were exposed to treatment for >6 months and 38% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 59% of patients receiving OPDIVO and ipilimumab. Study therapy was discontinued for adverse reactions in 31% of OPDIVO and ipilimumab patients. Fifty-four percent (54%) of patients receiving OPDIVO and ipilimumab had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO and ipilimumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. The most common adverse reactions (reported in ≥20% of patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of OPDIVO and ipilimumab-treated patients include increased lipase, anemia, increased creatinine, increased ALT, increased AST, hyponatremia, increased amylase, and lymphopenia.

Tables 25 and 26 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

Table 25: Adverse Reactions in >15% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-214

Adverse Reaction	OPDIVO and Ipilimumab (n=547)		Sunitinib (n=535)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	99	65	99	76
General				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				

Table 25: Adverse Reactions in >15% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-214

Adverse Reaction	OPDIVO and Ipilimumab (n=547)		Sunitinib (n=535)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Musculoskeletal pain[d]	37	4	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

[c] Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.

[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

Table 26: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO and Ipilimumab - CHECKMATE-214

Laboratory Abnormality	OPDIVO and Ipilimumab		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2	32	1
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6

Table 26: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO and Ipilimumab - CHECKMATE-214

Laboratory Abnormality	OPDIVO and Ipilimumab		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3	64	9
Lymphopenia	36	5	63	14

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

In addition, among patients with TSH ≤ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the OPDIVO and ipilimumab group compared to the sunitinib group (31% and 61%, respectively).

CHECKMATE-9ER

The safety of OPDIVO with cabozantinib was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received OPDIVO 240 mg over 30 minutes every 2 weeks with cabozantinib 40 mg orally once daily (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) *[see Clinical Studies (14.7)]*. Cabozantinib could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in OPDIVO and cabozantinib-treated patients. In this trial, 82% of patients in the OPDIVO and cabozantinib arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either OPDIVO or cabozantinib occurred in 20% of patients: 7% OPDIVO only, 8% cabozantinib only, and 6% both drugs due to same adverse reaction at the same time. Adverse reaction leading to dose interruption or reduction of either OPDIVO or cabozantinib occurred in 83% of patients: 3% OPDIVO only, 46% cabozantinib only, and 21% both drugs due to same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO and cabozantinib were diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9ER.

Table 27: Adverse Reactions in >15% of Patients Receiving OPDIVO and Cabozantinib - CHECKMATE-9ER

Adverse Reaction	OPDIVO and Cabozantinib (n=320)		Sunitinib (n=320)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System				
Dysgeusia	24	0	22	0

Table 27: Adverse Reactions in >15% of Patients Receiving OPDIVO and Cabozantinib - CHECKMATE-9ER

Adverse Reaction	OPDIVO and Cabozantinib (n=320)		Sunitinib (n=320)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Headache	16	0	12	0.6
Respiratory, Thoracic and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis.

Table 28: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Cabozantinib - CHECKMATE-9ER

Laboratory Abnormality	OPDIVO and Cabozantinib		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3

Table 28: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Cabozantinib - CHECKMATE-9ER

Laboratory Abnormality	OPDIVO and Cabozantinib		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and cabozantinib group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Previously Treated Renal Cell Carcinoma

CHECKMATE-025

The safety of OPDIVO was evaluated in CHECKMATE-025, a randomized open-label trial in 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.7)]*. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in OPDIVO-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

Rate of death on treatment or within 30 days of the last dose was 4.7% on the OPDIVO arm. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients. Forty-four percent (44%) of patients receiving OPDIVO had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. The most common adverse reactions (≥20%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite,

back pain, and arthralgia. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, increased triglycerides, and hyperkalemia. In addition, among patients with TSH < ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH >ULN in the OPDIVO group compared to the everolimus group (26% and 14%, respectively).

Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

Table 29: Adverse Reactions in >15% of Patients Receiving OPDIVO - CHECKMATE-025

Adverse Reaction	OPDIVO (n=406)		Everolimus (n=397)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	98	56	96	62
General				
Fatigue[a]	56	6	57	7
Pyrexia	17	0.7	20	0.8
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	34	0	38	0.5
Dyspnea/exertional dyspnea	27	3	31	2
Upper respiratory infection[b]	18	0	11	0
Gastrointestinal				
Nausea	28	0.5	29	1
Diarrhea[c]	25	2.2	32	1.8
Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5
Skin and Subcutaneous Tissue				
Rash[d]	28	1.5	36	1
Pruritus/generalized pruritus	19	0	14	0
Metabolism and Nutrition				
Decreased appetite	23	1.2	30	1.5
Musculoskeletal and Connective Tissue				
Arthralgia	20	1	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia, decreased activity, fatigue, and malaise.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral upper respiratory infection (URI).

[c] Includes colitis, enterocolitis, and gastroenteritis.

[d] Includes dermatitis, acneiform dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, erythema multiforme, and erythema.

Other clinically important adverse reactions in CHECKMATE-025 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

Investigations: weight decreased

Skin Disorders: palmar-plantar erythrodysesthesia

Table 30: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO - CHECKMATE-025

Laboratory Abnormality	OPDIVO		Everolimus	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	42	6	53	11
Anemia	39	8	69	16
Chemistry				
Increased creatinine	42	2	45	1.6
Increased AST	33	2.8	39	1.6
Increased alkaline phosphatase	32	2.3	32	0.8
Hyponatremia	32	7	26	6
Hyperkalemia	30	4	20	2.1
Hypocalcemia	23	0.9	26	1.3
Increased ALT	22	3.2	31	0.8
Hypercalcemia	19	3.2	6	0.3
Lipids				
Increased triglycerides	32	1.5	67	11
Increased cholesterol	21	0.3	55	1.4

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 259 to 401 patients) and everolimus group (range: 257 to 376 patients).

Classical Hodgkin Lymphoma

The safety of OPDIVO was evaluated in 266 adult patients with cHL (243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039 trials) *[see Clinical Studies (14.8)]*. Patients received OPDIVO 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity.

The median age was 34 years (range: 18 to 72), 98% of patients had received autologous HSCT, none had received allogeneic HSCT, and 74% had received brentuximab vedotin. The median number of prior systemic regimens was 4 (range: 2 to 15). Patients received a median of 23 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 11 months (range: 0 to 23 months).

Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last nivolumab dose, 2 from infection 8 to 9 months after completing nivolumab, and 6 from complications of allogeneic HSCT. Serious adverse reactions occurred in 26% of patients. Dose delay for an adverse reaction occurred in 34% of patients. OPDIVO was discontinued due to adverse reactions in 7% of patients.

The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. The most common adverse reactions (≥20%) among all patients were upper respiratory tract infection, fatigue, cough, diarrhea, pyrexia, musculoskeletal pain, rash, nausea, and pruritus.

Tables 31 and 32 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

Table 31: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Adverse Reaction[a]	OPDIVO (n=266)	
	All Grades (%)	Grades 3-4 (%)
Infections		
Upper respiratory tract infection[b]	44	0.8
Pneumonia/bronchopneumonia[c]	13	3.8
Nasal congestion	11	0
General		
Fatigue[d]	39	1.9
Pyrexia	29	<1
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
Gastrointestinal		

Table 31: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Adverse Reaction[a]	OPDIVO (n=266)	
	All Grades (%)	Grades 3-4 (%)
Diarrhea[e]	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain[f]	16	<1
Constipation	14	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[g]	26	1.1
Arthralgia	16	<1
Skin and Subcutaneous Tissue		
Rash[h]	24	1.5
Pruritus	20	0
Nervous System		
Headache	17	<1
Neuropathy peripheral[i]	12	<1
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	14	<1
Endocrine		
Hypothyroidism/thyroiditis	12	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes events occurring up to 30 days after last nivolumab dose, regardless of causality. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred up to 30 days after completing the initial nivolumab course.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and sinusitis.

[c] Includes pneumonia bacterial, pneumonia mycoplasmal, pneumocystis jirovecii pneumonia.

[d] Includes asthenia.

[e] Includes colitis.

[f] Includes abdominal discomfort and upper abdominal pain.

[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, and pain in extremity.

[h] Includes dermatitis, dermatitis acneiform, dermatitis exfoliative, and rash described as macular, papular, maculopapular, pruritic, exfoliative, or acneiform.

[i] Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy. These numbers are specific to treatment-emergent events.

Additional information regarding clinically important adverse reactions:

Immune-mediated pneumonitis: In CHECKMATE-205 and CHECKMATE-039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO (one Grade 3 and 12 Grade 2). The median time to onset was 4.5 months (range: 5 days to 12 months). All 13 patients received systemic corticosteroids, with resolution in 12. Four patients permanently discontinued OPDIVO due to pneumonitis. Eight patients continued OPDIVO (three after dose delay), of whom two had recurrence of pneumonitis.

Peripheral neuropathy: Treatment-emergent peripheral neuropathy was reported in 12% (31/266) of all patients receiving OPDIVO. Twenty-eight patients (11%) had new-onset peripheral neuropathy and 3 patients had worsening of neuropathy from baseline. The median time to onset was 50 (range: 1 to 309) days.

Complications of allogeneic HSCT after OPDIVO: Of 17 patients with cHL from the CHECKMATE-205 and CHECKMATE-039 trials who underwent allogeneic HSCT after treatment with OPDIVO, 6 patients (35%) died from transplant-related complications. Five deaths occurred in the setting of severe (Grade 3 to 4) or refractory GVHD. Hyperacute GVHD occurred in 2 patients (12%) and Grade 3 or higher GVHD was reported in 5 patients (29%). Hepatic VOD occurred in 1 patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

Table 32 summarizes laboratory abnormalities in patients with cHL. The most common (≥20%) treatment-emergent laboratory abnormalities included cytopenias, liver function abnormalities, and increased lipase. Other common findings (≥10%) included increased creatinine, electrolyte abnormalities, and increased amylase.

Table 32: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Laboratory Abnormality	**OPDIVO[a] (n=266)**	
	All Grades (%)[b]	**Grades 3-4 (%)[b]**
Hematology		
Leukopenia	38	4.5
Neutropenia	37	5
Thrombocytopenia	37	3
Lymphopenia	32	11
Anemia	26	2.6
Chemistry[c]		
Increased AST	33	2.6
Increased ALT	31	3.4
Increased lipase	22	9

Table 32: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Laboratory Abnormality	OPDIVO[a] (n=266)	
	All Grades (%)[b]	Grades 3-4 (%)[b]
Increased alkaline phosphatase	20	1.5
Hyponatremia	20	1.1
Hypokalemia	16	1.9
Increased creatinine	16	<1
Hypocalcemia	15	<1
Hyperkalemia	15	1.5
Hypomagnesemia	14	<1
Increased amylase	13	1.5
Increased bilirubin	11	1.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: range: 203 to 266 patients.

[b] Includes events occurring up to 30 days after last nivolumab dose. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred within 30 days of completing the initial nivolumab course.

[c] In addition, in the safety population, fasting hyperglycemia (all grade 1-2) was reported in 27 of 69 (39%) evaluable patients and fasting hypoglycemia (all grade 1-2) in 11 of 69 (16%).

Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.9)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously weekly). The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in OPDIVO-treated patients. In this trial, 18% of patients received OPDIVO for >6 months and 2.5% of patients received OPDIVO for >1 year.

The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the OPDIVO group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of

systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

Serious adverse reactions occurred in 49% of patients receiving OPDIVO. OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. The most common adverse reactions occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were cough and dyspnea. The most common laboratory abnormalities occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

Adjuvant Treatment of Urothelial Carcinoma (UC)

The safety of OPDIVO was evaluated in CHECKMATE-274, a randomized, double-blind, multicenter trial of adjuvant OPDIVO versus placebo in adult patients who had undergone radical resection of UC originating in the bladder or upper urinary tract (renal pelvis or ureter) and were at high risk of recurrence *[see Clinical Studies (14.10)]*. Patients received OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=351) or placebo (n=348) until recurrence or unacceptable toxicity for a maximum of 1 year. The median duration of OPDIVO treatment was 8.8 months (range: 0 to 12.5).

Serious adverse reactions occurred in 30% of OPDIVO patients. The most frequent serious adverse reaction reported in ≥2% of patients was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). OPDIVO was discontinued for adverse reactions in 18% of patients. OPDIVO was delayed for adverse reaction in 33% of patients.

The most common adverse reactions (reported in ≥20% of patients) were rash, fatigue, diarrhea, pruritus, musculoskeletal pain, and urinary tract infection.

Tables 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-274.

Table 33: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-274

Adverse Reaction	OPDIVO (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	36	1.7	19	0.3
Pruritus	30	0	16	0

Table 33: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-274

Adverse Reaction	OPDIVO (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue/Asthenia	36	1.1	32	0.3
Pyrexia	10	0.3	10	0.3
Gastrointestinal				
Diarrhea[b]	30	2.8	27	1.7
Nausea	16	0.6	13	0
Abdominal pain[c]	15	0.9	15	0.6
Constipation	13	0.3	15	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	28	0.6	24	0.9
Arthralgia	11	0.3	13	0
Infections				
Urinary tract infection[e]	22	6	23	9
Upper respiratory tract infection[f]	16	0.3	16	0.6
Endocrine				
Hyperthyroidism	11	0	1.1	0
Hypothyroidism	11	0	2.3	0
Renal and Urinary Disorders				
Renal dysfunction[g]	17	1.7	16	0.9
Respiratory, Thoracic and Mediastinal				
Cough[h]	14	0	11	0
Dyspnea[i]	11	0.3	6	0.3
Metabolism and Nutrition				
Decreased appetite	13	0.9	7	0.3
Nervous System Disorders				
Dizziness[j]	11	0.3	9	0
Hepatobiliary				
Hepatitis[k]	11	4	8	0.6

Toxicity was graded per NCI CTCAE v4.

[a] Includes acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, eczema asteatotic, eczema nummular, erythema, erythema multiforme, lichen sclerosus, lichenoid keratosis, pemphigoid, photosensitivity reaction, pigmentation disorder, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rosacea, skin exfoliation, skin lesion, skin reaction, toxic skin eruption, and urticaria.

[b] Includes colitis, colitis microscopic, diarrhea, duodenitis, enteritis, immune-mediated enterocolitis.

[c] Includes abdominal pain, abdominal discomfort, abdominal tenderness, lower and upper abdominal pain.

[d] Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

[e] Includes cystitis, escherichia urinary tract infection, pyelonephritis, pyelonephritis acute, pyelonephritis chronic, urethritis, urinary tract infection, urinary tract infection bacterial, urinary tract infection staphylococcal, and urosepsis.

[f] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis.

[g] Includes acute kidney injury, autoimmune nephritis, blood creatinine increased, glomerular filtration rate decreased, immune-mediated nephritis, nephritis, renal failure, and renal impairment.

[h] Includes cough, productive cough, and upper-airway cough syndrome.

[i] Includes dyspnea and exertional dyspnea.

[j] Includes dizziness, postural dizziness and vertigo.

[k] Includes aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, cholangitis, drug-induced liver injury, hepatic failure, hepatic function abnormal, hepatitis, hepatocellular injury, hyperbilirubinemia, gamma-glutamyl transferase increased, liver injury, and transaminases increased.

Table 34: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-274

Laboratory Abnormality	OPDIVO (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatinine	36	1.7	36	2.6
Increased amylase	34	8	23	3.2
Increased lipase	33	12	31	10
Hyperkalemia	32	5	30	6
Increased alkaline phosphatase	24	2.3	15	0.6
Increased AST	24	3.5	16	0.9
Increased ALT	23	2.9	15	0.6
Hyponatremia	22	4.1	17	1.8
Hypocalcemia	17	1.2	11	0.9
Hypomagnesemia	16	0	9	0
Hypercalcemia	12	0.3	8	0.3
Hematology				
Lymphopenia	33	2.9	27	1.5
Anemia	30	1.4	28	0.9

Table 34: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-274

Laboratory Abnormality	OPDIVO (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Neutropenia	11	0.6	10	0.3

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 322 to 348 patients) and placebo group (range: 312 to 341 patients).

First-line Treatment of Unresectable or Metastatic UC

The safety of OPDIVO was evaluated in CHECKMATE-901, a randomized, open-label trial in cisplatin-eligible patients with unresectable or metastatic UC *[see Clinical Studies (14.10)]*. Patients received either OPDIVO 360 mg with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by single-agent OPDIVO 480 mg every 4 weeks up to 2 years (n=304), or cisplatin and gemcitabine chemotherapy every 3 weeks for up to 6 cycles (n=288). Patients discontinuing cisplatin alone were permitted to switch to carboplatin.

Among patients who received OPDIVO with chemotherapy, the median duration of OPDIVO exposure was 7.4 months (range: 0.03 to 47.9 months). Serious adverse reactions occurred in 48% of patients receiving OPDIVO in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were urinary tract infection (4.9%), acute kidney injury (4.3%), anemia (3%), pulmonary embolism (2.6%), sepsis (2.3%), and platelet count decreased (2.3%). The most common adverse reactions (reported in ≥20% of patients) were nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy.

Fatal adverse reactions occurred in 3.6% of patients who received OPDIVO in combination with chemotherapy; these included sepsis (1%).

OPDIVO and/or chemotherapy were discontinued in 30% of patients and were delayed in 67% of patients for an adverse reaction.

Tables 35 and 36 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-901.

Table 35: Adverse Reactions Occurring in ≥10% of Treated Patients - CHECKMATE-901

Adverse Reaction	OPDIVO and Platinum-Doublet Chemotherapy (n=304)		Platinum-Doublet Chemotherapy (n=288)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Nausea	52	0.3	53	1

Table 35: Adverse Reactions Occurring in ≥10% of Treated Patients - CHECKMATE-901

Adverse Reaction	OPDIVO and Platinum-Doublet Chemotherapy (n=304)		Platinum-Doublet Chemotherapy (n=288)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Constipation	30	0	28	0.7
Vomiting	23	1.3	19	2.1
Diarrhea[a]	19	2	14	0
Abdominal pain[b]	14	0.3	9	0.3
General				
Fatigue[c]	48	3.9	43	4.2
Edema[d]	18	0	9	0.3
Pyrexia[e]	14	1	14	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[f]	33	3	21	0.3
Metabolism and Nutrition				
Decreased appetite	30	1.6	19	1
Skin and Subcutaneous Tissue				
Rash[g]	25	2.3	7	0.3
Pruritus	17	0.7	3.5	0
Nervous System Disorders				
Peripheral neuropathy[h]	20	0.7	14	0
Headache[i]	11	0	5	0
Infections				
Urinary tract infection[j]	19	8	18	8
Endocrine disorders				
Hypothyroidism[k]	17	0	0.3	0
Renal and Urinary Disorders				
Renal dysfunction[l]	14	6	11	1.7
Hematuria	11	1	7	1.4
Investigations				
Weight decreased	11	0.3	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes colitis, immune-mediated enterocolitis.

[b] Includes upper abdominal pain, lower abdominal pain, abdominal discomfort, epigastric discomfort, gastrointestinal pain, and hepatic pain.

[c] Includes asthenia.

[d] Includes peripheral edema, swelling, peripheral swelling, localized edema, swelling, face edema, testicular edema, gravitational edema, and edema genital.

[e] Includes hyperthermia, body temperature increased and hyperpyrexia.

[f] Includes back pain, arthralgia, bone pain, arthritis, musculoskeletal chest pain, non-cardiac chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

[g] Includes maculopapular rash, erythematous rash, macular rash, papular rash, pustular rash, acneiform dermatitis, dermatitis, allergic dermatitis, atopic dermatitis, exfoliative rash, eczema asteatotic, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis exfoliative generalized, and skin exfoliation.

[h] Includes paresthesia, peripheral sensory neuropathy, hypoesthesia, dysesthesia, neuralgia, hyperesthesia, peripheral motor neuropathy, polyneuropathy.

[i] Includes occipital neuralgia.

[j] Includes urosepsis, cystitis, pyelonephritis, pyelonephritis acute, urinary tract infection enterococcal, escherichia urinary tract infection.

[k] Includes blood stimulating hormone increased.

[l] Includes acute kidney injury, renal failure, renal impairment, glomerular filtration rate decreased, anuria, azotemia.

Table 36: Selected Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients - CHECKMATE-901

Laboratory Abnormality	OPDIVO and Platinum-Doublet Chemotherapy (n=304)		Platinum-Doublet Chemotherapy (n=288)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	88	21	80	21
Neutropenia	82	35	76	28
Lymphopenia	71	17	56	13
Thrombocytopenia	60	13	51	8
Chemistry				
Increased creatinine	53	2.4	42	1.1
Hypomagnesemia	48	3.8	39	1.5
Hyponatremia	43	13	39	8
Hyperglycemia	41	3.9	37	3.2
Hypocalcemia	36	2.1	24	1.1
Hyperkalemia	33	3.0	32	1.1
Increased amylase	32	4.2	23	3.6
Increased AST	31	2.4	17	0.7
Increased ALT	29	2.4	19	0.7

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 289-301 patients) and chemotherapy group (range: 265-281 patients).

Previously Treated Advanced or Metastatic UC

The safety of OPDIVO was evaluated in CHECKMATE-275, a single arm trial in which 270 patients with locally advanced or metastatic UC had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.10)]*. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a dose interruption for an adverse reaction.

Fourteen patients (5.2%) died from causes other than disease progression. This includes 4 patients (1.5%) who died from pneumonitis or cardiovascular failure which was attributed to treatment with OPDIVO. Serious adverse reactions occurred in 54% of patients. OPDIVO was discontinued for adverse reactions in 17% of patients.

The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Tables 37 and 38 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

Table 37: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	**OPDIVO (n=270)**	
	All Grades (%)	**Grades 3-4 (%)**
Adverse Reaction	99	51
General		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[a]	30	2.6
Arthralgia	10	0.7
Metabolism and Nutrition		
Decreased appetite	22	2.2

Table 37: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
Gastrointestinal		
Nausea	22	0.7
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[b]	13	1.5
Vomiting	12	1.9
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
Infections		
Urinary tract infection/escherichia/fungal urinary tract infection	17	7
Skin and Subcutaneous Tissue		
Rash[c]	16	1.5
Pruritus	12	0
Endocrine		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

[b] Includes abdominal discomfort, lower and upper abdominal pain.

[c] Includes dermatitis, dermatitis acneiform, dermatitis bullous, and rash described as generalized, macular, maculopapular, or pruritic.

[d] Includes autoimmune thyroiditis, blood TSH decrease, blood TSH increase, hyperthyroidism, hypothyroidism, thyroiditis, thyroxine decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased, tri-iodothyronine increased.

Table 38: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275

Laboratory Abnormality	OPDIVO[a]	
	All Grades (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	42	2.4

Table 38: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275

Laboratory Abnormality	OPDIVO[a]	
	All Grades (%)	Grades 3-4 (%)
Hyponatremia	41	11
Increased creatinine	39	2
Increased alkaline phosphatase	33	5.5
Hypocalcemia	26	0.8
Increased AST	24	3.5
Increased lipase	20	7
Hyperkalemia	19	1.2
Increased ALT	18	1.2
Increased amylase	18	4.4
Hypomagnesemia	16	0
Hematology		
Lymphopenia	42	9
Anemia	40	7
Thrombocytopenia	15	2.4
Leukopenia	11	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: range: 84 to 256 patients.

MSI-H or dMMR Metastatic Colorectal Cancer

Treatment of MSI-H or dMMR mCRC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab, or as a single agent, was evaluated in CHECKMATE-8HW, a randomized, open-label, three arm trial in immunotherapy naive patients with MSI-H or dMMR mCRC *[see Clinical Studies (14.11)]*. Patients received one of the following:

- OPDIVO 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then OPDIVO 480 mg every 4 weeks.
- OPDIVO 240 mg every 2 weeks for 6 doses, then OPDIVO 480 mg every 4 weeks.
- Investigator's choice chemotherapy: mFOLFOX or FOLFIRI *[see Clinical Studies (14.11)]*.

In the OPDIVO and ipilimumab arm, the median duration of exposure to OPDIVO was 20.5 months (range: 0 to 35.9 months), 70% of patients were exposed for >6 months and 63% were exposed for >1 year. In the OPDIVO arm, the median duration of exposure to OPDIVO was 16.4 months (range: 0 to 36 months), 64% of patients were exposed for >6 months and 54% were exposed for >1 year.

Serious adverse reactions occurred in 46% of patients receiving OPDIVO in combination with ipilimumab, and 39% of patients receiving OPDIVO alone. The most frequent serious adverse reactions reported in ≥1% of patients who received OPDIVO with ipilimumab were adrenal insufficiency (2.8%), hypophysitis (2.8%), diarrhea (2.0%), abdominal pain (2.0%), small intestinal obstruction (2.0%), pneumonia (1.7%), acute kidney injury (1.4%), immune mediated enterocolitis (1.4%), pneumonitis (1.4%), colitis (1.1%), large intestinal obstruction (1.1%), and urinary tract infection (1.1%). The most frequent serious adverse reactions reported in >1% of patients who received OPDIVO, as a single agent, were intestinal obstruction (2.3%), acute kidney injury (1.7%), COVID-19 (1.7%), abdominal pain (1.4%), diarrhea (1.4%), ileus (1.4%), subileus (1.4%), pulmonary embolism (1.4%), adrenal insufficiency (1.1%) and pneumonia (1.1%).

Fatal adverse reactions occurred in 2 (0.6%) patients who received OPDIVO in combination with ipilimumab; these included myocarditis, and pneumonitis (1 each). Fatal adverse reactions occurring in 3 (0.9%) patients who received OPDIVO as a single agent; these included pneumonitis (n=2) and myasthenia gravis.

OPDIVO and/or ipilimumab were permanently discontinued in 19% of patients receiving the combination. The most frequent adverse reactions (>1%) leading to permanent discontinuation were adrenal insufficiency (1.4%), immune mediated enterocolitis (1.1%), and pneumonitis (1.1%). OPDIVO was permanently discontinued in 13% of patients receiving single agent OPDIVO. Adverse reactions leading to the delay of OPDIVO and/or ipilimumab occurred in 48% of patients receiving the combination; single agent OPDIVO was delayed in 37% of patients due to adverse reactions.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with ipilimumab were fatigue, diarrhea, pruritus, abdominal pain, musculoskeletal pain, and nausea. The most common adverse reactions reported in ≥20% of patients treated with OPDIVO as a single agent, were fatigue, diarrhea, abdominal pain, pruritus, and musculoskeletal pain.

Tables 39 and 40 summarize selected adverse reactions and selected laboratory abnormalities for OPDIVO in combination with ipilimumab and the single agent OPDIVO arms respectively, in CHECKMATE-8HW.

Table 39: Adverse Reactions[a] in ≥10% in Patients with a Difference Between Arms of >5% for All Grades in CHECKMATE-8HW

Adverse Reaction	OPDIVO and ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or4 (%)
Gastrointestinal				
Diarrhea[a]	35	4.5	30	3.4
Skin and Subcutaneous Tissue				
Pruritus	30	0	23	0
Musculoskeletal and Connective Tissue				
Arthralgia	20	0.6	15	0.6

Table 39: Adverse Reactions[a] in ≥10% in Patients with a Difference Between Arms of >5% for All Grades in CHECKMATE-8HW

Adverse Reaction	OPDIVO and ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or4 (%)
Endocrine				
Hypothyroidism	18	0.6	10	0
Hyperthyroidism	12	0	5	0

Toxicity was graded per NCI CTCAE v5.

[a] Includes colitis, diarrhea, enterocolitis, immune mediated enterocolitis

Table 40: Laboratory Values Worsening from Baseline[a] in ≥10% of Patients and a Difference Between Arms of >5% for All Grades - CHECKMATE-8HW

Laboratory Abnormality[a]	OPDIVO and Ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	Grades 3-or 4 (%)	All Grades (%)	Grades 3 or -4 (%)
Hematology				
Lymphocytes decreased	30	5	37	4
Neutrophils decreased	21	1.7	12	0.6
Chemistry				
Lipase increased	44	10	32	11
Amylase increased	41	4.6	33	5
ALT increased	39	3.5	32	1.4
AST increased	38	3.2	29	1.4
Sodium decreased	36	3.2	30	2.3
Creatinine increased	32	2	25	1.4
Potassium increased	29	1.2	35	0.9
Glucose decreased	17	0	12	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 108 to 343 patients) or nivolumab group (range: 102 to 348 patients).

MSI-H or dMMR mCRC After Progression Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial *[see Clinical Studies (14.11)]*. In CHECKMATE-142, 74 patients with mCRC received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or until intolerable toxicity and 119 patients with mCRC received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity.

In the OPDIVO with ipilimumab cohort, serious adverse reactions occurred in 47% of patients. Treatment was discontinued in 13% of patients and delayed in 45% of patients for an adverse reaction. The most frequent serious adverse reactions reported in ≥2% of patients were

colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Tables 41 and 42 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-142. Based on the design of CHECKMATE-142, the data below cannot be used to identify statistically significant differences between the two cohorts summarized below for any adverse reaction.

Table 41: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142

Adverse Reaction	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	54	5	49	6
Pyrexia	24	0	36	0
Edema[b]	12	0	7	0
Gastrointestinal				
Diarrhea	43	2.7	45	3.4
Abdominal pain[c]	34	2.7	30	5
Nausea	34	1.4	26	0.8
Vomiting	28	4.1	20	1.7
Constipation	20	0	15	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	28	1.4	36	3.4
Arthralgia	19	0	14	0.8
Respiratory, Thoracic and Mediastinal				
Cough	26	0	19	0.8
Dyspnea	8	1	13	1.7
Skin and Subcutaneous Tissue				
Rash[e]	23	1.4	25	4.2
Pruritus	19	0	28	1.7
Dry Skin	7	0	11	0
Infections				
Upper respiratory tract infection[f]	20	0	9	0
Endocrine				

Table 41: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142

Adverse Reaction	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hyperglycemia	19	2.7	6	1
Hypothyroidism	5	0	14	0.8
Hyperthyroidism	4	0	12	0
Nervous System				
Headache	16	0	17	1.7
Dizziness	14	0	11	0
Metabolism and Nutrition				
Decreased appetite	14	1.4	20	1.7
Psychiatric				
Insomnia	9	0	13	0.8
Investigations				
Weight decreased	8	0	10	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema and peripheral swelling.

[c] Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.

[d] Includes back pain, pain in extremity, myalgia, neck pain, and bone pain.

[e] Includes dermatitis, dermatitis acneiform, and rash described as maculo-papular, erythematous, and generalized.

[f] Includes nasopharyngitis and rhinitis.

Clinically important adverse reactions reported in <10% of patients receiving OPDIVO with ipilimumab were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

Table 42: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-142

Laboratory Abnormality	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	50	7	42	9
Lymphopenia	36	7	25	6
Neutropenia	20	4.3	18	0
Thrombocytopenia	16	1.4	26	0.9
Chemistry				

Table 42: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-142

Laboratory Abnormality	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphatase	37	2.8	28	5
Increased lipase	33	19	39	12
Increased ALT	32	2.8	33	12
Increased AST	31	1.4	40	12
Hyponatremia	27	4.3	26	5
Hypocalcemia	19	0	16	0
Hypomagnesemia	17	0	18	0
Increased amylase	16	4.8	36	3.4
Increased bilirubin	14	4.2	21	5
Hypokalemia	14	0	15	1.8
Increased creatinine	12	0	25	3.6
Hyperkalemia	11	0	23	0.9

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Number of evaluable patients ranges from 62 to 71 for the OPDIVO cohort and from 87 to 114 for the OPDIVO and ipilimumab cohort.

Hepatocellular Carcinoma

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-9DW, a randomized, open-label trial in adult patients with unresectable or metastatic HCC *[see Clinical Studies (14.12)]*. Patients received OPDIVO in combination with ipilimumab (n=332) or investigator's choice of lenvatinib (n=275) or sorafenib (n=50) at the following dosage:

- OPDIVO 1 mg/kg administered intravenously over 30 minutes in combination with ipilimumab 3 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single-agent OPDIVO at 480 mg administered intravenously over 30 minutes every 4 weeks, or
- Investigator's choice:
  - Lenvatinib 8 mg orally daily (if body weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg), or
  - Sorafenib 400 mg orally twice daily

In the OPDIVO and ipilimumab arm, the median duration of exposure to OPDIVO was 4.7 months (range: <0.1 to 24.4 months), 45% were exposed for >6 months and 30% were exposed for >1 year.

Serious adverse reactions occurred in 53% of patients treated with OPDIVO in combination with ipilimumab. The most frequent non-liver-related serious adverse reactions reported in ≥2% of patients who received OPDIVO in combination with ipilimumab were diarrhea/colitis (4.5%), gastrointestinal hemorrhage (3%), and rash (2.4%).

Liver-related serious adverse reactions occurred in 17% of patients treated with OPDIVO in combination with ipilimumab, including Grade 3-4 events in 16% of patients. The most frequently reported all grade liver-related serious adverse reactions occurring in ≥1% of patients who received OPDIVO in combination with ipilimumab were immune-mediated hepatitis (3%), increased AST/ALT (3%), hepatic failure (2.4%), ascites (2.4%), and hepatotoxicity (1.2%).

Fatal adverse reactions occurred in 12 (3.6%) patients who received OPDIVO in combination with ipilimumab; these included 4 (1.2%) patients who died due to immune-mediated or autoimmune hepatitis and 4 (1.2%) patients who died of hepatic failure.

Permanent discontinuations of OPDIVO due to an adverse reaction occurred in 27% of patients. Adverse reactions leading to permanent discontinuation of OPDIVO in >1% of patients included immune-mediated hepatitis (1.8%), diarrhea/colitis (1.8%), hepatic failure (1.2%).

Dosage interruptions of OPDIVO due to an adverse reaction occurred in 62% of patients. Adverse reactions which required dosage interruption in >5% of patients included increased AST (13%), increased ALT (11%), and diarrhea/colitis (8%).

The most common (>20%) adverse reactions were rash, pruritus, fatigue, and diarrhea.

Tables 43 and 44 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9DW.

Table 43: Adverse Reactions Occurring in ≥10% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	36	3.6	15	1.2
Pruritus	34	1.5	7	0.3
General				
Fatigue[a]	33	2.4	39	4
Pyrexia[a]	15	0.6	9	1.5
Edema[a]	13	1.2	13	1.5

Table 43: Adverse Reactions Occurring in ≥10% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea[a]	25	6	39	3.4
Abdominal pain[a]	14	1.2	27	2.5
Nausea	10	0.3	16	0.9
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	17	0.6	23	0.3
Arthralgia	12	0.3	13	0.6
Metabolism and Nutrition				
Decreased appetite	16	1.2	28	1.8
Endocrine				
Hypothyroidism[a]	14	0	27	0
Hyperthyroidism	11	0.6	1.5	0
Respiratory, Thoracic and Mediastinal				
Cough[a]	13	0	8	0

Toxicity was graded per NCI CTCAE v5

[a] Represents a composite of multiple related terms.

Clinically important adverse reactions reported in <10% of patients who received OPDIVO with ipilimumab were hyperglycemia (8%), adrenal insufficiency (4.2%), pneumonitis (2.7%), and pancreatitis (2.4%).

Table 44: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	62	29	51	14
Increased ALT	61	17	46	9
Increased lipase	58	16	39	5
Decreased albumin	48	0.9	57	0.6

Table 44: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hyponatremia	45	6	42	3.8
Hyperglycemia	44	15	32	2.1
Increased bilirubin	44	10	44	8
Increased amylase	41	6	26	1
Increased alkaline phosphatase	36	1.2	38	5
Hypocalcemia	29	0.9	46	0
Increased creatinine	26	2.4	23	0.6
Hypokalemia	21	2.1	20	2.6
Hematology				
Anemia	44	5	40	3.8
Lymphopenia	40	6.1	40	8
Thrombocytopenia	27	4	44	4.8
Neutropenia	24	4	32	3.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 168 to 331 patients) and lenvatinib or sorafenib group (range: 145 to 315 patients).

Previously Treated Hepatocellular Carcinoma

The safety of OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of CHECKMATE-040, a multicenter, multiple-cohort, open-label trial *[see Clinical Studies (14.12)]* who progressed on or were intolerant to sorafenib. OPDIVO and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent OPDIVO 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the OPDIVO and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

The most frequent serious adverse reactions (reported in ≥4% of patients) were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Tables 45 and 46 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-040.

Table 45: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue		
Rash	53	8
Pruritus	53	4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain	41	2
Arthralgia	10	0
Gastrointestinal		
Diarrhea	39	4
Abdominal pain	22	6
Nausea	20	0
Ascites	14	6
Constipation	14	0
Dry mouth	12	0
Dyspepsia	12	2
Vomiting	12	2
Stomatitis	10	0
Respiratory, Thoracic and Mediastinal		
Cough	37	0
Dyspnea	14	0
Pneumonitis	10	2
Metabolism and Nutrition		
Decreased appetite	35	2
General		
Fatigue	27	2
Pyrexia	27	0

Table 45: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Malaise	18	2
Edema	16	2
Influenza-like illness	14	0
Chills	10	0
Nervous System		
Headache	22	0
Dizziness	20	0
Endocrine		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4
Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

Clinically important adverse reactions reported in <10% of patients who received OPDIVO with ipilimumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Table 46: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Lymphopenia	53	13
Anemia	43	4.3
Neutropenia	43	9
Leukopenia	40	2.1
Thrombocytopenia	34	4.3
Chemistry		
Increased AST	66	40
Increased ALT	66	21
Increased bilirubin	55	11
Increased lipase	51	26
Hyponatremia	49	32
Hypocalcemia	47	0
Increased alkaline phosphatase	40	4.3
Increased amylase	38	15
Hypokalemia	26	2.1
Hyperkalemia	23	4.3
Increased creatinine	21	0
Hypomagnesemia	11	0

In patients who received OPDIVO with ipilimumab, virologic breakthrough occurred in 4 of 28 (14%) patients and 2 of 4 (50%) patients with active HBV or HCV at baseline, respectively. HBV virologic breakthrough was defined as at least a 1 log increase in HBV DNA for those patients with detectable HBV DNA at baseline. HCV virologic breakthrough was defined as a 1 log increase in HCV RNA from baseline.

Esophageal Cancer

Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

The safety of OPDIVO was evaluated in CHECKMATE-577, a randomized, placebo-controlled, double-blinded, multicenter trial in 792 treated patients with completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following chemoradiotherapy (CRT) *[see Clinical Studies (14.13)]*. The trial excluded patients who did not receive concurrent CRT prior to surgery, had stage IV resectable disease, autoimmune

disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Patients received either OPDIVO 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Patients were treated until disease recurrence, unacceptable toxicity, or for up to 1-year total duration. The median duration of exposure was 10.1 months (range: <0.1 to 14 months) in OPDIVO-treated patients and 9 months (range: <0.1 to 15 months) in placebo-treated patients. Among patients who received OPDIVO, 61% were exposed for >6 months and 54% were exposed for >9 months.

Serious adverse reactions occurred in 33% of patients receiving OPDIVO. A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal adverse reaction of myocardial infarction occurred in one patient who received OPDIVO.

OPDIVO was discontinued in 12% of patients and was delayed in 28% of patients for an adverse reaction.

Tables 47 and 48 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-577.

Table 47: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - CHECKMATE-577

Adverse Reaction	OPDIVO (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	96	34	93	32
Gastrointestinal				
Diarrhea	29	0.9	29	0.8
Nausea	23	0.8	21	0
Abdominal Pain[a]	17	0.8	20	1.5
Vomiting	15	0.6	16	1.2
Dysphagia	13	0.8	17	3.5
Dyspepsia[b]	12	0.2	16	0.4
Constipation	11	0	12	0
General				
Fatigue[c]	34	1.3	29	1.5
Respiratory, Thoracic and Mediastinal				
Cough[d]	20	0.2	21	0.4
Dyspnea[e]	12	0.8	12	0.4
Skin and Subcutaneous Tissue				

Table 47: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - CHECKMATE-577

Adverse Reaction	OPDIVO (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	96	34	93	32
Rash[f]	21	0.9	10	0.4
Pruritus	13	0.4	6	0
Investigations				
Weight decreased	13	0.4	9	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[g]	21	0.6	20	0.8
Arthralgia	10	0.2	8	0
Metabolism and Nutrition				
Decreased appetite	15	0.9	10	0.8
Endocrine				
Hypothyroidism	11	0	1.5	0

[a] Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.
[b] Includes gastroesophageal reflux.
[c] Includes asthenia.
[d] Includes productive cough.
[e] Includes dyspnea exertional.
[f] Includes rash pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, exfoliative rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic.
[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, spinal pain.

Table 48: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-577

Laboratory Abnormality	OPDIVO (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased AST	27	2.1	22	0.8
Increased alkaline phosphatase	25	0.8	18	0.8
Increased albumin	21	0.2	18	0
Increased ALT	20	1.9	16	1.2

Table 48: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-577

Laboratory Abnormality	OPDIVO (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased amylase	20	3.9	13	1.3
Hyponatremia	19	1.7	12	1.2
Hyperkalemia	17	0.8	15	1.6
Hypokalemia	12	1	11	1.2
Transaminases increased[b]	11	1.5	6	1.2
Hematology				
Lymphopenia	44	17	35	12
Anemia	27	0.8	21	0.4
Neutropenia	24	1.5	23	0.4

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 163 to 526 patients) and Placebo group (range: 86 to 256 patients).
[b] Includes alanine aminotransferase increased, aspartate aminotransferase increased.

First-line Treatment of Unresectable Advanced or Metastatic ESCC

The safety of OPDIVO in combination with chemotherapy or in combination with ipilimumab was evaluated in CHECKMATE-648, a randomized, active-controlled, multicenter, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC *[see Clinical Studies (14.13)]*. Patients received one of the following treatments:

- OPDIVO 240 mg on days 1 and 15, 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).

Among patients who received OPDIVO with chemotherapy, the median duration of exposure was 5.7 months (range: 0.1 to 30.6 months). Among patients who received OPDIVO and ipilimumab, the median duration of exposure was 2.8 months (range: 0 to 24 months).

Serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy and in 69% of patients receiving OPDIVO in combination with ipilimumab. The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with ipilimumab were pneumonia (10%), pyrexia (4.3%),

pneumonitis (4%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%).

Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury and in 5 (1.6%) patients who received OPDIVO in combination with ipilimumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

OPDIVO and/or chemotherapy were discontinued in 39% of patients and were delayed in 71% of patients for an adverse reaction. OPDIVO and/or ipilimumab were discontinued in 23% of patients and were delayed in 46% of patients for an adverse reaction.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were nausea, decreased appetite, fatigue, constipation, stomatitis, diarrhea, and vomiting. The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with ipilimumab were rash, fatigue, pyrexia, nausea, diarrhea, and constipation.

Tables 49 and 50 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-648.

Table 49: Adverse Reactions in ≥10% of Patients - CHECKMATE-648

Adverse Reaction	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal						
Nausea	65	4.2	22	0.6	56	2.6
Constipation	44	1.0	20	0.3	43	1
Stomatitis[a]	44	9	11	0.6	35	3
Diarrhea	29	2.9	22	1.9	20	2
Vomiting	23	2.3	15	1.6	19	3
Dysphagia	14	7	12	5	12	4.9
Abdominal pain[b]	13	1.9	10	0.9	11	0.7
Metabolism and Nutrition						
Decreased appetite	51	7	17	4	50	6
General						
Fatigue[c]	47	3.5	28	2.5	41	4.9
Pyrexia[d]	19	0.3	23	0.9	12	0.3

Table 49: Adverse Reactions in ≥10% of Patients - CHECKMATE-648

Adverse Reaction	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Edema[e]	16	0	7	0	13	0
Nervous System						
Peripheral neuropathy[f]	18	1.3	2.8	0	13	1
Psychiatric						
Insomnia	16	0	8	0	10	0.3
Skin and Subcutaneous Tissue						
Rash[g]	16	0.6	31	3.1	7	0
Pruritus	11	0	17	0.9	3.6	0
Alopecia	10	0			11	0
Respiratory, Thoracic and Mediastinal						
Cough[h]	16	0.3	13	0.3	13	0.3
Infections and Infestations						
Pneumonia[i]	13	5	14	8	10	2.6
Endocrine						
Hypothyroidism	7	0	14	0	0.3	0
Investigations						
Weight decreased	12	0.6	12	1.9	11	1
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[j]	11	0.3	14	0.6	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.

[b] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.

[c] Includes asthenia and malaise.

[d] Includes tumor associated fever.

[e] Includes swelling, generalized edema, edema peripheral, and peripheral swelling.

[f] Includes hyperesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

[g] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, and rash pruritic.

[h] Includes productive cough.

[i] Includes organizing pneumonia, pneumonia bacterial, and pneumonia pseudomonal.

[j] Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

Table 50: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-648

Laboratory Abnormality	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology						
Anemia	81	21	52	7	66	14
Lymphopenia	67	23	50	13	44	8
Neutropenia	61	18	13	1.3	48	13
Leukopenia	53	11			39	5
Thrombocytopenia	43	3.3	12	1	29	2.8
Chemistry						
Hyponatremia	52	15	45	11	40	8
Hypocalcemia	43	3	32	0	23	0.7
Increased creatinine	41	2.3	15	0.7	31	0.7
Hypomagnesemia	35	1.7	15	0	25	1.8
Hyperglycemia	34	0	43	4.3	36	0.8
Hyperkalemia	33	2.3	23	1.6	24	0.7
Hypokalemia	29	9	19	5	17	6
Increased alkaline phosphatase	26	1.3	31	3.3	15	0
Increased AST	23	3.3	39	6	11	1.4
Increased ALT	23	2.3	33	6	8	0.7
Hypoglycemia	18	0.4	15	1.2	7	0
Hypercalcemia	11	2.6	15	2	8	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO with cisplatin and 5-FU group (range: 60 to 305 patients), OPDIVO and ipilimumab group (range: 59 to 307 patients) or cisplatin and 5-FU group (range: 56 to 283 patients).

Previously-Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

The safety of OPDIVO was evaluated in ATTRACTION-3, a randomized, active-controlled, open-label, multicenter trial in 209 patients with unresectable advanced, recurrent or metastatic ESCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based chemotherapy *[see Clinical Studies (14.13)]*. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had

autoimmune disease, used systemic corticosteroids or immunosuppressants, had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients received OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=209) or investigator's choice: docetaxel 75 mg/m^2 intravenously every 3 weeks (n=65) or paclitaxel 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off (n=143). Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 2.6 months (range: 0 to 29.2 months) in OPDIVO-treated patients and 2.6 months (range: 0 to 21.4 months) in docetaxel- or paclitaxel-treated patients. Among patients who received OPDIVO, 26% were exposed for >6 months and 10% were exposed for >1 year.

Serious adverse reactions occurred in 38% of patients receiving OPDIVO. Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%).

OPDIVO was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction.

Tables 51 and 52 summarize the adverse reactions and laboratory abnormalities, respectively, in ATTRACTION-3.

Table 51: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - ATTRACTION-3

Adverse Reaction	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	22	1.9	28	1
Pruritus	12	0	7	0
Metabolism and Nutrition				
Decreased appetite[b]	21	1.9	35	5
Gastrointestinal				
Diarrhea[c]	18	1.9	17	1.4
Constipation	17	0	19	0
Nausea	11	0	20	0.5
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	17	0	26	1.4
Infections				

Table 51: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - ATTRACTION-3

Adverse Reaction	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Upper respiratory tract infection[e]	17	1	14	0
Pneumonia[f]	13	5	19	9
Respiratory, Thoracic and Mediastinal				
Cough[g]	16	0	14	0.5
General				
Pyrexia[h]	16	0.5	19	0.5
Fatigue[i]	12	1.4	27	4.8
Blood and Lymphatic System				
Anemia[j]	13	8	30	13
Endocrine				
Hypothyroidism[k]	11	0	1.4	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes urticaria, drug eruption, eczema, eczema asteatotic, eczema nummular, palmar-plantar erythrodysesthesia syndrome, erythema, erythema multiforme, blister, skin exfoliation, Stevens-Johnson syndrome, dermatitis, dermatitis described as acneiform, bullous, or contact, and rash described as maculo-papular, generalized, or pustular.

[b] Includes hypophagia, and food aversion.

[c] Includes colitis.

[d] Includes spondylolisthesis, periarthritis, musculoskeletal chest pain, neck pain, arthralgia, back pain, myalgia, pain in extremity, arthritis, bone pain, and periarthritis calcarea.

[e] Includes influenza, influenza like illness, pharyngitis, nasopharyngitis, tracheitis, and bronchitis and upper respiratory infection with bronchitis.

[f] Includes pneumonia aspiration, pneumonia bacterial, and lung infection. Two patients (1.0%) died of pneumonia in the OPDIVO treatment arm. Two patients (1.0%) died of pneumonia in the chemotherapy treatment arm; these deaths occurred with paclitaxel only.

[g] Includes productive cough.

[h] Includes tumor-associated fever.

[i] Includes asthenia.

[j] Includes hemoglobin decreased, and iron deficiency anemia.

[k] Includes blood thyroid stimulating hormone increased.

Table 52: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - ATTRACTION-3

Laboratory Abnormality	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatinine	78	0.5	68	0.5
Hyperglycemia	52	5	62	5
Hyponatremia	42	11	50	12
Increased AST	40	6	30	1
Increased alkaline phosphatase	33	4.8	24	1.0
Increased ALT	31	5	22	1.9
Hypercalcemia	22	6	14	2.9
Hyperkalemia	22	0.5	31	1
Hypoglycemia	14	1.4	14	0.5
Hypokalemia	11	2.9	13	3.4
Hematology				
Lymphopenia	46	19	72	43
Anemia	42	9	71	17
Leukopenia	11	0.5	79	45

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (209 patients) and Docetaxel or Paclitaxel group (range: 207 to 208 patients).

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

The safety of OPDIVO in combination with chemotherapy was evaluated in CHECKMATE-649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma *[see Clinical Studies (14.14)]*. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive or had untreated central nervous system (CNS) metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated with OPDIVO in combination with chemotherapy or chemotherapy until disease progression, unacceptable toxicity, or up to 2 years. The median duration of exposure was

6.8 months (range: 0 to 33.5 months) in OPDIVO and chemotherapy-treated patients. Among patients who received OPDIVO and chemotherapy, 54% were exposed for >6 months and 28% were exposed for >1 year.

Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation. Serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy. OPDIVO and/or chemotherapy were discontinued in 44% of patients and at least one dose was withheld in 76% of patients due to an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were peripheral neuropathy, nausea, fatigue, diarrhea, vomiting, decreased appetite, abdominal pain, constipation, and musculoskeletal pain.

Tables 53 and 54 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-649.

Table 53: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Chemotherapy - CHECKMATE-649

Adverse Reaction	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	69	98	59
Nervous System				
Peripheral neuropathy[a]	53	7	46	4.8
Headache	11	0.8	6	0.3
Gastrointestinal				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain[b]	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis[c]	17	1.8	13	0.8

Table 53: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Chemotherapy - CHECKMATE-649

Adverse Reaction	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[d]	44	7	40	5
Pyrexia[e]	19	1	11	0.4
Edema[f]	12	0.5	8	0.1
Metabolism and Nutrition				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia[g]	14	0.3	9	0.3
Investigations				
Weight decreased	17	1.3	15	0.7
Increased lipase	14	7	8	3.7
Increased amylase	12	3.1	5	0.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[h]	20	1.3	14	2
Skin and Subcutaneous Tissue				
Rash[i]	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8
Respiratory, Thoracic and Mediastinal				
Cough[j]	13	0.1	9	0
Infections and Infestations				
Upper respiratory tract infection[k]	10	0.1	7	0.1

Toxicity was graded per NCI CTCAE v4.

[a] Includes dysesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

[b] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.

[c] Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.

[d] Includes asthenia.

[e] Includes tumor associated fever.

[f] Includes swelling, generalized edema, edema peripheral, and peripheral swelling.

[g] Includes blood albumin decreased.

[h] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

[i] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash vesicular.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, and rhinitis.

Table 54: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-649

Laboratory Abnormality	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Neutropenia	73	29	62	23
Leukopenia	69	12	59	9
Thrombocytopenia	68	7	63	4.4
Anemia	59	14	60	10
Lymphopenia	59	12	49	9
Chemistry				
Increased AST	52	4.6	47	1.9
Hypocalcemia	42	1.6	37	1
Hyperglycemia	41	3.9	38	2.7
Increased ALT	37	3.4	30	1.9
Hyponatremia	34	6	24	5
Hypokalemia	27	7	24	4.8
Hyperbilirubinemia	24	2.8	21	2
Increased creatinine	15	1	9	0.5
Hyperkalemia	14	1.4	11	0.7
Hypoglycemia	12	0.7	9	0.2
Hypernatremia	11	0.5	7.1	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and mFOLFOX6 or CapeOX group (407 to 767 patients) or mFOLFOX6 or CapeOX group (range: 405 to 735 patients).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPDIVO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye: Vogt-Koyanagi-Harada (VKH) syndrome

Complications of OPDIVO Treatment After Allogeneic HSCT: Treatment refractory, severe acute and chronic GVHD

Blood and lymphatic system disorders: Hemophagocytic lymphohistiocytosis (HLH) (including fatal cases), autoimmune hemolytic anemia (including fatal cases)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the

breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO *[see Use in Specific Populations (8.1)]*.

Contraception

OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for 5 months following the last dose.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO have been established in pediatric patients aged 12 years and older for the following indications: as a single agent and in combination with ipilimumab for the treatment of unresectable or metastatic melanoma, as a single agent for the adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma in combination with ipilimumab for the treatment of MSI-H or dMMR unresectable and metastatic CRC, and as a single agent for the treatment of MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for these indications is supported by evidence from adequate and well-controlled studies in adults with melanoma or MSI-H or dMMR mCRC and additional pharmacokinetic data in pediatric patients. Nivolumab exposure in pediatric patients 12 years and older is comparable to that of adults and the courses of melanoma and MSI-H or dMMR mCRC are similar in pediatric patients aged 12 years and older to that of adults to allow extrapolation of safety and efficacy *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1, 14.11)]*.

The safety and effectiveness of OPDIVO have not been established for pediatric patients younger than 12 years old with melanoma or MSI-H or dMMR mCRC.

The safety and effectiveness of OPDIVO have not been established in pediatric patients with non-small cell lung cancer, malignant pleural mesothelioma, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal cancer and esophageal adenocarcinoma.

8.5 Geriatric Use

Single Agent

Of 3569 patients with melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, ESCC, and esophageal or gastroesophageal junction cancer who were randomized to single agent OPDIVO in clinical studies, 41% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients *[see Clinical Studies (14.1, 14.2, 14.5, 14.7, 14.10, 14.13, 14.14)]*.

In patients with cHL, recurrent head and neck SCC, or dMMR or MSI-H metastatic CRC (mCRC) who were treated with single agent OPDIVO in clinical studies did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.8, 14.9, 14.11)]*.

OPDIVO in Combination with Ipilimumab

Of the 314 patients with melanoma who were randomized to OPDIVO in combination with ipilimumab, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients *[see Clinical Studies (14.1)]*.

Of the 576 patients with NSCLC who were randomized to OPDIVO in combination with ipilimumab, 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received OPDIVO with ipilimumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to OPDIVO in combination with ipilimumab, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see Clinical Studies (14.3)]*.

Of the 303 patients with malignant pleural mesothelioma who were randomized to OPDIVO in combination with ipilimumab, 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received OPDIVO with ipilimumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and the discontinuation rate due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to OPDIVO in combination with ipilimumab *[see Clinical Studies (14.6)]*.

Of the 550 patients with renal cell carcinoma who were randomized to OPDIVO in combination with ipilimumab, 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported *[see Clinical Studies (14.7)]*.

Of the 354 patients with dMMR or MSI-H metastatic CRC (mCRC) who were randomized to OPDIVO in combination with ipilimumab, 44% were 65 years or older and 14% were 75 years or older. Of the 353 patients randomized to OPDIVO, as a single agent, 45% were 65 years or older and 13% were 75 years or older. There was a higher incidence of any Grade 3 or 4 adverse reactions (55%) in patients aged 65 years or older receiving OPDIVO in combination with ipilimumab compared to those younger than 65 receiving the combination (42%). There was also a higher

incidence of any Grade 3 or 4 adverse reactions (55%) in patients aged 65 years or older receiving OPDIVO in combination with ipilimumab relative to patients aged 65 years or older receiving single-agent OPDIVO (41%). There was a similar incidence of any Grade 3 or 4 adverse reactions in patients receiving single-agent OPDIVO aged 65 years or older (41%) relative to patients younger than 65 years (45%). Patients 65 years or older who received OPDIVO with ipilimumab discontinued treatment due to adverse reaction at a higher rate (23%) relative to patients 65 years or older receiving nivolumab (15%). No overall differences in effectiveness were reported between elderly patients and younger patients receiving either OPDIVO in combination with ipilimumab or single-agent OPDIVO *[see Clinical Studies (14.11)]*.

Of the 335 patients with unresectable hepatocellular carcinoma who were randomized to OPDIVO in combination with ipilimumab, 52% were 65 years or older and 14% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients, however, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received OPDIVO with ipilimumab (53% and 27%, respectively).

Of the 49 patients with hepatocellular carcinoma who were treated with OPDIVO in combination with ipilimumab, 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of OPDIVO in combination with ipilimumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.12)]*.

Of the 325 patients with ESCC who were randomized to OPDIVO in combination with ipilimumab, 43% were 65 years old or older and 7% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (38%) relative to all patients who received OPDIVO with ipilimumab (23%). For patients aged 75 years or older who received chemotherapy, the discontinuation rate due to adverse reactions was 33% relative to 23% for all patients *[see Clinical Studies (14.13)]*.

OPDIVO in Combination with Platinum-Containing Chemotherapy

Of the 179 patients with NSCLC who were randomized to OPDIVO in combination with platinum-doublet chemotherapy, 48% were 65 years old or older and 6% were 75 years old or older. No overall differences in safety or effectiveness were reported between patients older and younger than 65 years *[see Clinical Studies (14.3)]*.

Of the 229 patients with NSCLC who were randomized to OPDIVO 360 mg in combination with platinum-doublet chemotherapy every 3 weeks for up to 4 cycles, followed by OPDIVO 480 mg every 4 weeks, 56% were 65 years old or older and 7% were 75 years old or older. No overall differences in safety or effectiveness were reported between patients older and younger than 65 years.

Of the 1,110 patients with ESCC, GC, GEJC, or EAC who were randomized to OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy, 42% were 65 years

or older and 10% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients *[see Clinical Studies (14.13, 14.14)]*.

Of the 304 patients with UC who were treated with OPDIVO in combination with gemcitabine and platinum-doublet chemotherapy, 40% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age and over and younger patients. Clinical studies of OPDIVO with platinum-doublet chemotherapy did not include sufficient numbers of patients aged 75 years and over to determine whether safety and effectiveness differs compared to younger patients. *[see Clinical Studies (14.10)]*.

OPDIVO in Combination with Ipilimumab and Platinum-Doublet Chemotherapy

Of the 361 patients with NSCLC who were randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older *[see Clinical Studies (14.5)]*.

OPDIVO in Combination with Cabozantinib

Of the 320 patients with renal cell carcinoma who were treated with OPDIVO in combination with cabozantinib, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients *[see Clinical Studies (14.7)]*.

11 DESCRIPTION

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles.

OPDIVO (nivolumab) injection for intravenous use is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

12.2 Pharmacodynamics

There are no clinically significant exposure-response relationships for efficacy or safety for nivolumab monotherapy across the approved dosing regimens, regardless of cancer type.

12.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single agent OPDIVO and OPDIVO with ipilimumab. The PK of nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO as a 60-minute intravenous infusion every 2 or 3 weeks. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold.

Distribution

The geometric mean volume of distribution at steady state (Vss) and coefficient of variation (CV%) is 6.8 L (27.3%).

Elimination

Nivolumab clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state.

The geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%).

Specific Populations

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR $\geq$ 15 mL/min/1.73 m^2), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

Pediatric Patients

The exposures of nivolumab, as monotherapy or in combination with ipilimumab, in pediatric patients 12 years of age or older are within range of those in adults at the recommended dosage *[see Dosage and Administration (2.2)]*.

Drug Interaction Studies

When OPDIVO 3 mg/kg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 3 weeks, the CL of nivolumab and ipilimumab were unchanged compared to nivolumab or ipilimumab administered alone.

When OPDIVO 1 mg/kg every 3 weeks was administered in combination with ipilimumab 3 mg/kg every 3 weeks, the CL of nivolumab was increased by 29% compared to OPDIVO administered alone and the CL of ipilimumab was unchanged compared to ipilimumab administered alone.

When OPDIVO 3 mg/kg every 2 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab was increased by 30% compared to ipilimumab administered alone.

When OPDIVO 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab increased by 22% compared to ipilimumab administered alone.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of OPDIVO or of other nivolumab products.

Anti-drug antibody and neutralizing antibody responses were monitored throughout the treatment period where the benefit to risk ratio was assessed. Incidence of anti-drug antibodies and neutralizing antibodies are presented in Table 55.

Table 55: OPDIVO Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Incidence

Treatment Regimen[a]	Indication(s)	ADA	NAb[b]
OPDIVO as a single agent	Multiple[c]	11% (229/2,085)	7% (15/229)
OPDIVO with ipilimumab for 4 doses followed by OPDIVO as a single agent	Melanoma	38% (149/394)	12% (18/149)
	HCC	56% (27/48)	41% (11/27)
	RCC and CRC	26% (132/516)	3% (4/132)
OPDIVO with ipilimumab	Malignant Pleural Mesothelioma	26% (69/269)	2.9% (2/69)
	NSCLC	37% (180/491)	3.9% (7/180)
OPDIVO with ipilimumab and 2 cycles of platinum-doublet chemotherapy	NSCLC	34% (104/308)	8% (8/104)

[a] Details of each treatment regimen are described in Section 14 *[see Clinical Studies (14)]*.

[b] NAb incidence is reported among the subset of patients positive for ADA.

[c] Includes unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, cHL, recurrent or metastatic SCCHN, and UC indications.

ADA = treatment-emergent anti-nivolumab antibodies, NAb = neutralizing antibodies, HCC = hepatocellular carcinoma, RCC = renal cell carcinoma, CRC = colorectal cancer, NSCLC = non-small cell lung cancer.

Effects of Anti-Drug Antibodies

Presence of treatment-emergent anti-nivolumab antibodies increased nivolumab clearance by up to 20% after administration of nivolumab as monotherapy or in combination with ipilimumab. These anti-drug antibody-associated pharmacokinetic changes were not considered to be clinically significant. There was no identified clinically significant effect of anti-drug antibodies on incidence of infusion-related reactions. The effects of anti-drug antibodies on effectiveness have not been fully characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis–infected PD-1 knockout mice exhibit

markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

CHECKMATE-037 (NCT01721746) was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive OPDIVO 3 mg/kg intravenously every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 intravenously every 3 weeks and paclitaxel 175 mg/m^2 intravenously every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

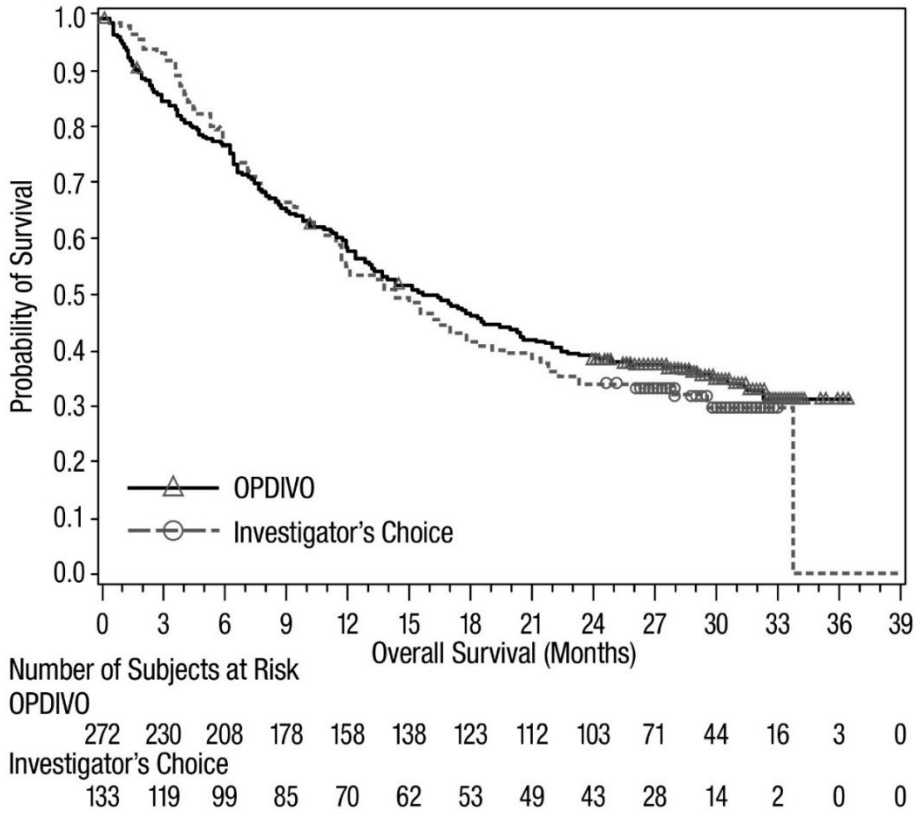
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with OPDIVO, the median age was 58 years (range: 25 to 88), 65% of patients were male, 98% were White, and the ECOG performance score was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval [CI]: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 87% had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were responses in patients with and without BRAF V600 mutation-positive melanoma. A total of 405 patients were randomized and the median duration of OS was 15.7 months (95% CI: 12.9, 19.9) in OPDIVO-treated patients compared to 14.4 months (95% CI: 11.7, 18.2) (HR 0.95; 95.54% CI: 0.73, 1.24) in patients assigned to investigator's choice of treatment. Figure 1 summarizes the OS results.

Figure 1: Overall Survival - CHECKMATE-037*



* The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies, and differences in baseline factors.

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and ORR per RECIST v1.1.

The trial population characteristics were: median age was 65 years (range: 18 to 87), 59% were male, and 99.5% were White. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 ≥5% tumor cell membrane expression (35%), and history of brain metastasis (4%). More patients in the OPDIVO arm had an ECOG performance status of 0 (71% vs. 58%).

CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 56 and Figure 2.

Table 56: Efficacy Results - CHECKMATE-066

	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median (months) (95% CI)	NR[a]	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[b]	0.42 (0.30, 0.60)	
p-value[c,d]	<0.0001	
Progression-free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median (months) (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI)[b]	0.43 (0.34, 0.56)	
p-value[c,d]	<0.0001	
Overall Response Rate	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

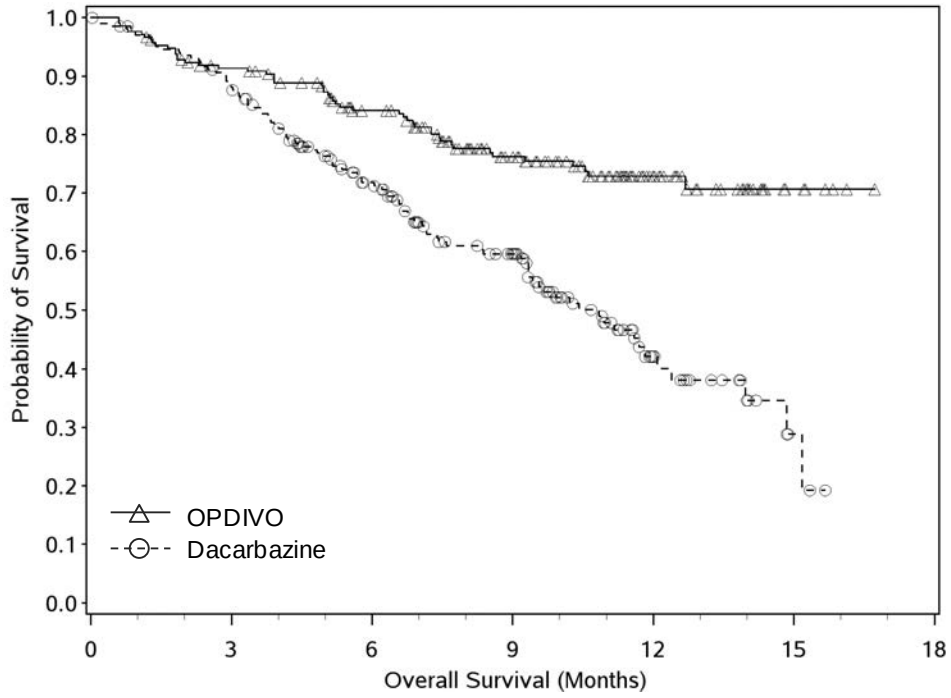
[a] Not Reached.

[b] Based on a stratified proportional hazards model.

[c] Based on stratified log-rank test.

[d] p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

Figure 2: Overall Survival - CHECKMATE-066



Number at Risk							
OPDIVO	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

CHECKMATE-067

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in 945 patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO and ipilimumab, OPDIVO, or ipilimumab. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

- OPDIVO 1 mg/kg with ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO and ipilimumab arm),
- OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO arm), or
- Ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks (ipilimumab arm).

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the AJCC staging system (M0, M1a, M1b vs. M1c). Tumor assessments were conducted 12 weeks

after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The major efficacy outcome measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 57 and Figure 3.

Table 57: Efficacy Results - CHECKMATE-067

	OPDIVO and Ipilimumab (n=314)	**OPDIVO (n=316)**	**Ipilimumab (n=315)**
Overall Survival[a]			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.55 (0.44, 0.69)	0.63 (0.50, 0.78)	
p-value[c, d]	<0.0001	<0.0001	
Progression-free Survival[a]			
Disease progression or death	151 (48%)	174 (55%)	234 (74%)
Median (months) (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.42 (0.34, 0.51)	0.57 (0.47, 0.69)	
p-value[c, e]	<0.0001	<0.0001	
Confirmed Overall Response Rate[a]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[f]	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
Duration of Response			
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

[a] OS results are based on final OS analysis with 28 months of minimum follow-up; PFS (co-primary endpoint) and ORR (secondary endpoint) results were based on primary analysis with 9 months of minimum follow-up.

[b] Based on a stratified proportional hazards model.

[c] Based on stratified log-rank test.

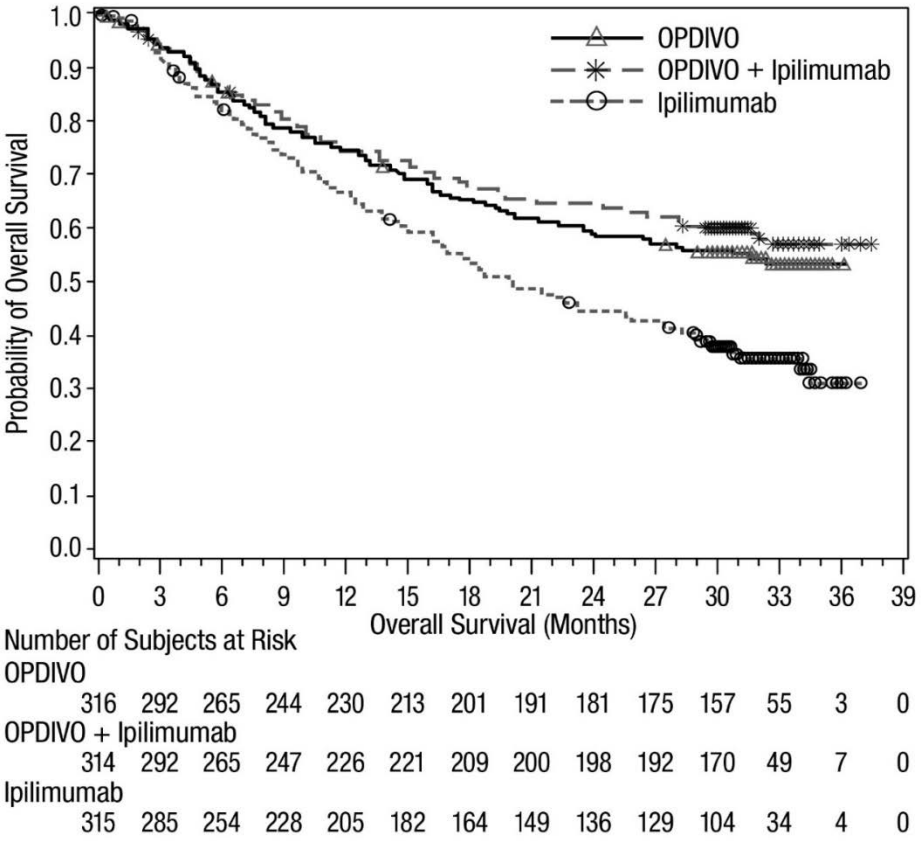
[d] If the maximum of the two OS p-values is less than 0.04 (a significance level assigned by the Hochberg procedure), then both p-values are considered significant.

[e] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.

[f] Based on the stratified Cochran-Mantel-Haenszel test.

[+] Censored observation

Figure 3: Overall Survival - CHECKMATE-067



Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the OPDIVO and ipilimumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the OPDIVO arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the OPDIVO and ipilimumab arm, 6.9 months (95% CI: 4.3, 9.5) in the OPDIVO arm, and 2.9 months (95% CI: 2.8, 3.2) in the ipilimumab arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥24 months was 55% in the OPDIVO and ipilimumab arm, 56% in the OPDIVO arm, and 39% in the ipilimumab arm.

14.2 Adjuvant Treatment of Melanoma

CHECKMATE-76K

CHECKMATE-76K (NCT04099251) was a randomized, double-blind trial in 790 patients with completely resected Stage IIB/C melanoma. Patients were randomized (2:1) to receive OPDIVO 480 mg or placebo by intravenous infusion every 4 weeks for up to 1 year or until disease recurrence or unacceptable toxicity. Enrollment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node within 12 weeks prior to randomization, and ECOG performance status of 0 or 1. The trial excluded patients with ocular/uveal or mucosal melanoma, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery. Randomization was stratified by AJCC 8th staging system edition (T3b vs. T4a vs. T4b). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurred first and as assessed by the investigator. Tumor assessments were conducted every 26 weeks during years 1-3 and every 52 weeks thereafter until year 5.

The trial population characteristics were: median age 62 years (range: 19 to 92), 61% were male, 98% were White, 0.4% Black or African American, 0.1% Asian, and 1.1% race unknown, 2.2% Hispanic or Latino, 58% Not Hispanic or Latino, 40% ethnicity unknown, and 94% had an ECOG performance status of 0. Sixty one percent had stage IIB and 39% had stage IIC melanoma.

CHECKMATE-76K demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the placebo arm. Efficacy results are shown in Table 58 and Figure 4.

Table 58: Efficacy Results - CHECKMATE-76K

	OPDIVO n=526	**Placebo n=264**
Recurrence-free Survival		
Number of events, n (%)	66 (13%)	69 (26%)
Median (months) [b] (95% CI)	NR[a] (28.5, NR)	NR[a] (21.6, NR)
Hazard ratio[c] (95% CI) p-value[d]	0.42 (0.30, 0.59) p<0.0001	

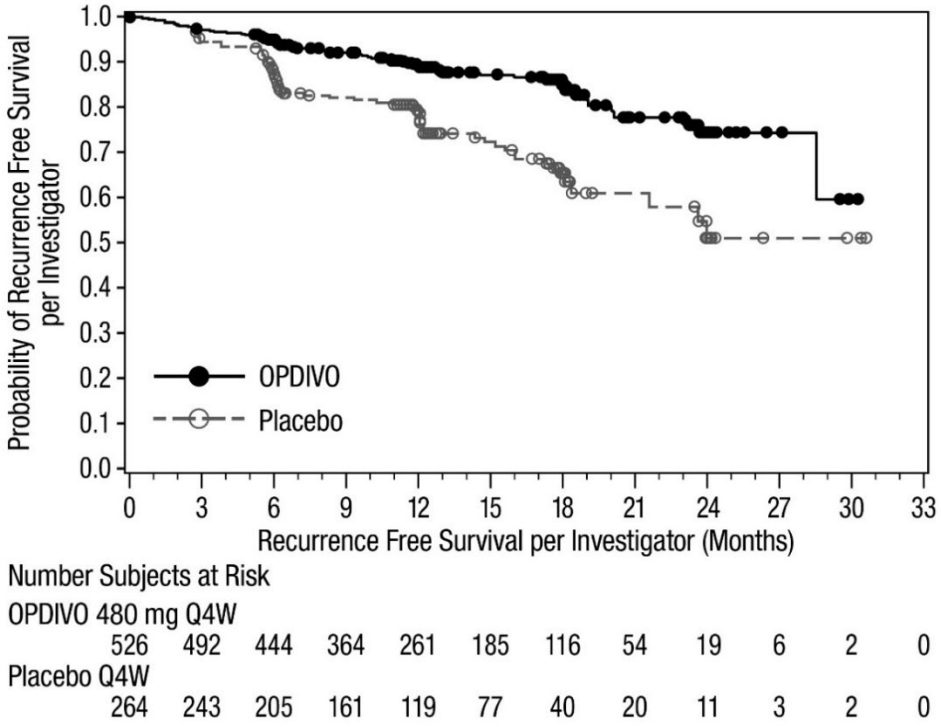
[a] Not reached.

[b] Based on Kaplan-Meier estimates.

[c] Hazard Ratio is OPDIVO over placebo based on a stratified Cox proportional hazard model.

[d] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value <0.033.

Figure 4: Recurrence-free Survival - CHECKMATE-76K



CHECKMATE-238

CHECKMATE-238 (NCT02388906) was a randomized, double-blind trial in 906 patients with completely resected Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or ipilimumab 10 mg/kg intravenously every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior to randomization. The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs. negative/indeterminate) and AJCC stage (Stage IIIB/C vs. Stage IV M1a-M1b vs. Stage IV M1c). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurs first and as assessed by the investigator. Patients underwent imaging for tumor recurrence every 12 weeks for the first 2 years then every 6 months thereafter.

The trial population characteristics were: median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600

mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 59 and Figure 5.

Table 59: Efficacy Results - CHECKMATE-238

	OPDIVO N=453	**Ipilimumab 10 mg/kg N=453**
Recurrence-free Survival		
Number of events, n (%)	154 (34%)	206 (45%)
Median (months) (95% CI)	NR[a]	NR[a] (16.56, NR[a])
Hazard ratio[b] (95% CI) p-value[c,d]	0.65 (0.53, 0.80) p<0.0001	
Overall Survival		
Number of events, n (%)[e]	100 (22%)	111 (25%)
Median (months) (95% CI)	NR[a]	NR[a]
Hazard ratio[b] (95% CI) p-value	0.87 (0.67, 1.14) 0.3148	

[a] Not reached.

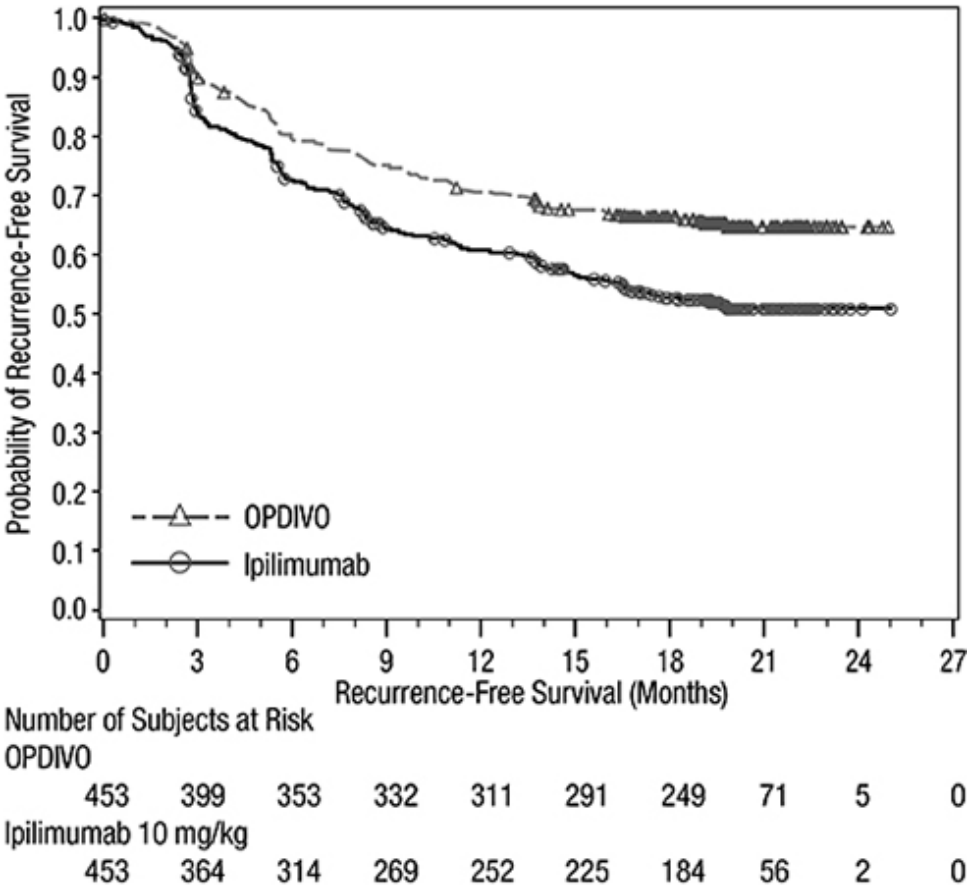
[b] Based on a stratified proportional hazards model.

[c] Based on a stratified log-rank test.

[d] p-value is compared with 0.0244 of the allocated alpha for this analysis.

[e] At the time of the final OS analysis, fewer overall survival events were observed than originally anticipated (approximately 302).

Figure 5: Recurrence-free Survival - CHECKMATE-238



14.3 Neoadjuvant Treatment of Resectable (Tumors ≥4 cm or Node Positive) Non-Small Cell Lung Cancer

CHECKMATE-816 (NCT02998528) was a randomized, open label trial in patients with resectable NSCLC. The trial included patients with resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA NSCLC (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria), ECOG performance status 0 or 1, and measurable disease (per RECIST version 1.1). Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients were randomized to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered intravenously every 3 weeks for up to 3 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-doublet chemotherapy consisted of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous

histology). In the platinum-doublet chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology).

Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). Tumor assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The major efficacy outcome measures were event-free survival (EFS) based on blinded independent central review (BICR) assessment and pathologic complete response (pCR) as evaluated by blinded independent pathology review (BIPR). Additional efficacy outcome measures included OS.

A total of 358 patients were randomized to receive either OPDIVO in combination with platinum-doublet chemotherapy (n=179) or platinum-doublet chemotherapy (n=179). The median age was 65 years (range: 34 to 84) with 51% of patients ≥65 years and 7% of patients ≥75 years, 50% were Asian, 47% were White, 2% were Black, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% had tumors with PD-L1 expression ≥1%; 35% had stage IB/II and 64% had stage IIIA disease; 51% had tumors with squamous histology and 49% had tumors with non-squamous histology; and 89% were former/current smokers.

Eighty-three percent of patients in the OPDIVO in combination with platinum-doublet chemotherapy arm had definitive surgery compared to 75% of patients in the platinum-doublet chemotherapy arm.

The study demonstrated statistically significant improvements in EFS and pCR. Efficacy results are presented in Table 60 and Figure 6.

Table 60: Efficacy Results - CHECKMATE-816

	OPDIVO and Platinum-Doublet Chemotherapy (n=179)	**Platinum-Doublet Chemotherapy (n=179)**
Event-free Survival (EFS) per BICR		
Events (%)	64 (35.8)	87 (48.6)
Median (months)[a] (95% CI)	31.6 (30.2, NR)	20.8 (14.0, 26.7)
Hazard Ratio[b] (95% CI)	0.63 (0.45, 0.87)	
Stratified log-rank p-value[c]	0.0052	
Pathologic Complete Response (pCR) per BIPR		
Number of patients with pCR	43	4
pCR Rate (%), (95% CI)[d]	24.0 (18.0, 31.0)	2.2 (0.6, 5.6)

Table 60: Efficacy Results - CHECKMATE-816

	OPDIVO and Platinum-Doublet Chemotherapy (n=179)	Platinum-Doublet Chemotherapy (n=179)
Estimated treatment difference (95% CI)[e]	21.6 (15.1, 28.2)	
p-value[f]	<0.0001	

Minimum follow-up for EFS was 21 months.

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

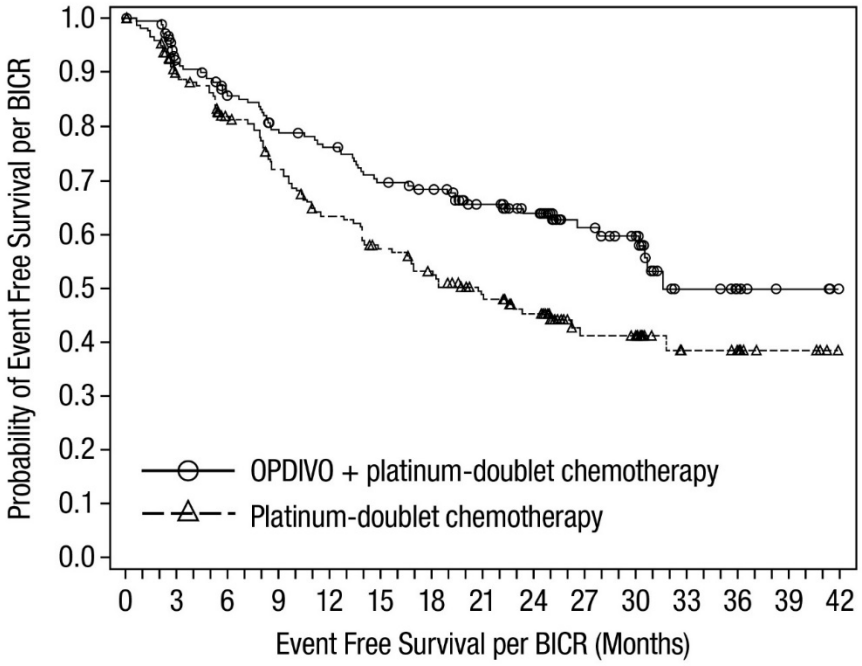
[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.

[d] Based on Clopper and Pearson method.

[e] Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

[f] From stratified CMH test.

Figure 6: Event-Free Survival - CHECKMATE-816



At the time of the EFS analysis, 26% of the patients had died. A prespecified interim analysis for OS resulted in a HR of 0.57 (95% CI: 0.38, 0.87), which did not cross the boundary for statistical significance.

14.4 Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

The efficacy of OPDIVO, in combination with platinum-doublet chemotherapy, followed by surgery, and continued adjuvant treatment with OPDIVO as a single agent, was investigated in CHECKMATE-77T (NCT04025879), a randomized, double-blind trial in 461 patients with resectable NSCLC. The trial included patients with resectable, suspected or histologically confirmed Stage IIA (>4 cm) to IIIB (T3-T4 N2) NSCLC (per the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual), and ECOG performance status 0 or 1. Patients with unresectable or metastatic NSCLC, EGFR mutations or known ALK translocations, brain metastasis, Grade 2 or greater peripheral neuropathy, interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomization was stratified by tumor PD-L1 expression level (≥1% versus <1% versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumor histology (squamous versus nonsquamous).

Patients were randomized (1:1) to receive either:

- Neoadjuvant OPDIVO 360 mg administered intravenously over 30 minutes in combination with one of the following platinum-doublet chemotherapy regimens every 3 weeks for four cycles:
    - Paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology)
    - Pemetrexed 500 mg/m^2, and cisplatin 75 mg/m^2 or carboplatin AUC 5 or AUC 6 (nonsquamous histology)
    - Cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 (squamous histology).

  Within 90 days after the surgery, OPDIVO 480 mg was administered intravenously over 30 minutes every 4 weeks.

or

- Neoadjuvant placebo administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy *(see above)* every 3 weeks for four cycles. Within 90 days after the surgery, placebo was administered intravenously over 30 minutes every 4 weeks.

All study medications were administered via intravenous infusion. Treatment continued until disease progression, recurrence, or unacceptable toxicity for up to 13 cycles (1 year). Tumor assessments were performed every 12 weeks for 2 years, then every 24 weeks for up to 5 years or until disease recurrence or progression was confirmed by BICR.

The trial was not designed to isolate the effect of OPDIVO in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included overall survival (OS), pathologic complete response (pCR), and major pathologic response (MPR).

The median age was 66 years (range: 35 to 86); 71% were male; 72% were White, 25% were Asian, 1.7% were Black, and 1.5% were mixed race/ race unknown/ not reported; and 6% were Hispanic or Latino. Baseline ECOG performance status was 0 (62%) or 1 (38%); 56% had tumors with PD-L1 expression ≥1% and 40% had tumors with PD-L1 expression <1%; 35% had stage II and 64% had stage III disease; 23% had N1 disease and 39% had N2 disease; 51% had tumors with squamous histology and 49% had tumors with nonsquamous histology; and 90% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant OPDIVO arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm.

The study demonstrated a statistically significant improvement in EFS for patients treated with neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by single agent OPDIVO compared with patients randomized to placebo in combination with platinum-doublet chemotherapy followed by placebo. Efficacy results are presented in Table 61 and Figure 7.

Table 61: Efficacy Results - CHECKMATE-77T

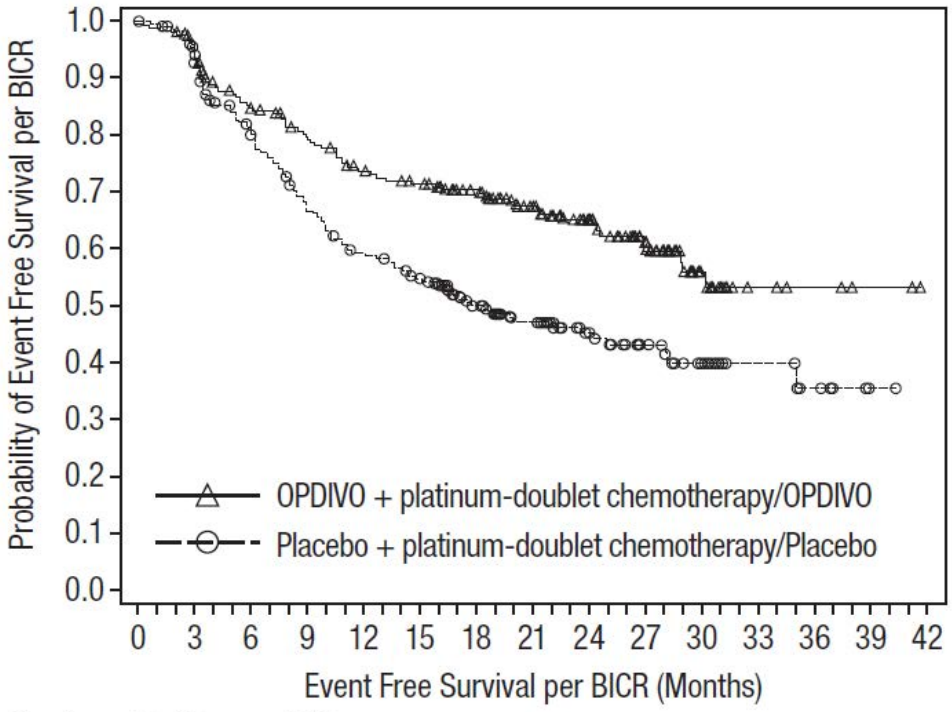
	Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy/Adjuvant OPDIVO (n=229)	**Neoadjuvant Placebo and Platinum-Doublet Chemotherapy/Adjuvant Placebo (n=232)**
Event-free Survival (EFS) per BICR		
Events (%)	76 (33%)	113 (49%)
Median (months)[a] (95% CI)	NR (28.9, NR)	18.4 (13.6, 28.1)
Hazard Ratio[b] (95% CI)	0.58 (0.43, 0.78)	
Stratified log-rank p-value[c]	0.00025	

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0264.

Figure 7: Event-Free Survival - CHECKMATE-77T



In a pre-specified descriptive analysis, the pCR rate was 25% (95% CI: 20, 31) in the OPDIVO arm and 4.7% (95% CI: 2.4, 8) in the placebo arm.

At the time of the EFS analysis, OS data were immature.

14.5 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Ipilimumab

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [IASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior

to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). The evaluation of efficacy relied on the comparison between:

- OPDIVO 3 mg/kg administered intravenously over 30 minutes every 2 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks; or
- Platinum-doublet chemotherapy

Chemotherapy regimens consisted of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or pemetrexed (500 mg/m^2) and carboplatin (AUC 5 or 6) for non-squamous NSCLC or gemcitabine (1000 or 1250 mg/m^2) and cisplatin (75 mg/m^2) or gemcitabine (1000 mg/m^2) and carboplatin (AUC 5) (gemcitabine was administered on Days 1 and 8 of each cycle) for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

In Part 1a, a total of 793 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers.

The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the OPDIVO and ipilimumab arm compared with the platinum-doublet chemotherapy arm. The OS results are presented in Table 62 and Figure 8.

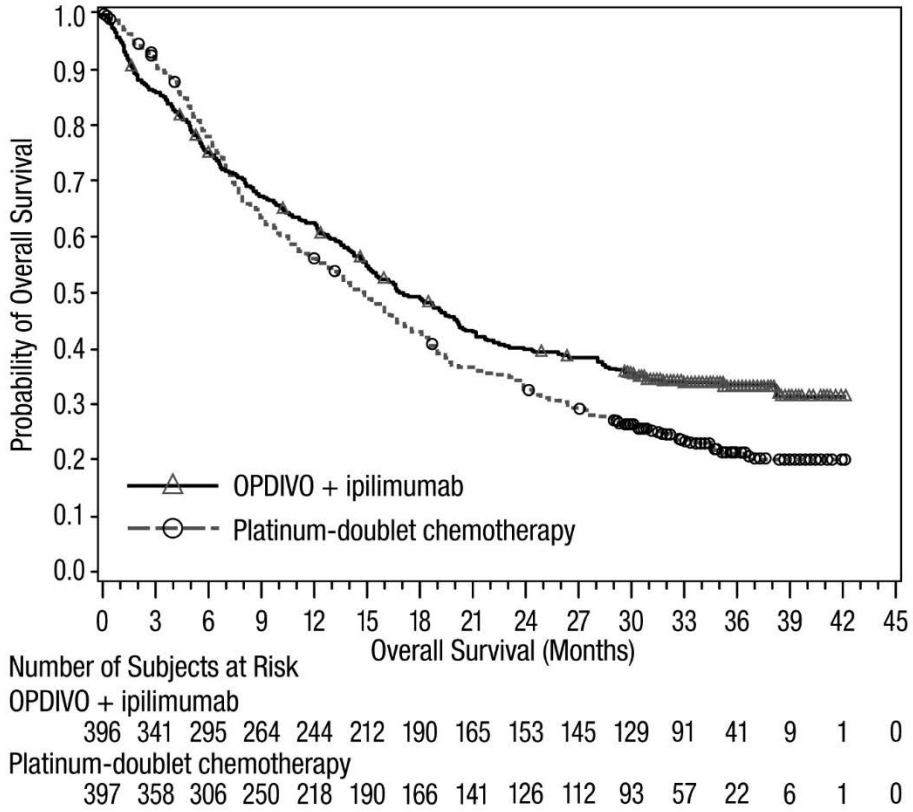
Table 62: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	OPDIVO and Ipilimumab (n=396)	Platinum-Doublet Chemotherapy (n=397)
Overall Survival		
Events (%)	258 (65%)	298 (75%)
Median (months)[a] (95% CI)	17.1 (15, 20.1)	14.9 (12.7, 16.7)
Hazard ratio (95% CI)[b]	0.79 (0.67, 0.94)	
Stratified log-rank p-value	0.0066	

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

Figure 8: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227



BICR-assessed PFS showed a HR of 0.82 (95% CI: 0.69, 0.97), with a median PFS of 5.1 months (95% CI: 4.1, 6.3) in the OPDIVO and ipilimumab arm and 5.6 months (95% CI: 4.6, 5.8) in the platinum-doublet chemotherapy arm. The BICR-assessed confirmed ORR was 36% (95% CI: 31, 41) in the OPDIVO and ipilimumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the OPDIVO and ipilimumab arm was 23.2 months and 6.2 months in the platinum-doublet chemotherapy arm.

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks, ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks, and platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2, or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 63.

Table 63: Efficacy Results - CHECKMATE-9LA

	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=361)	**Platinum-Doublet Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

[a] Based on a stratified Cox proportional hazard model.

[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

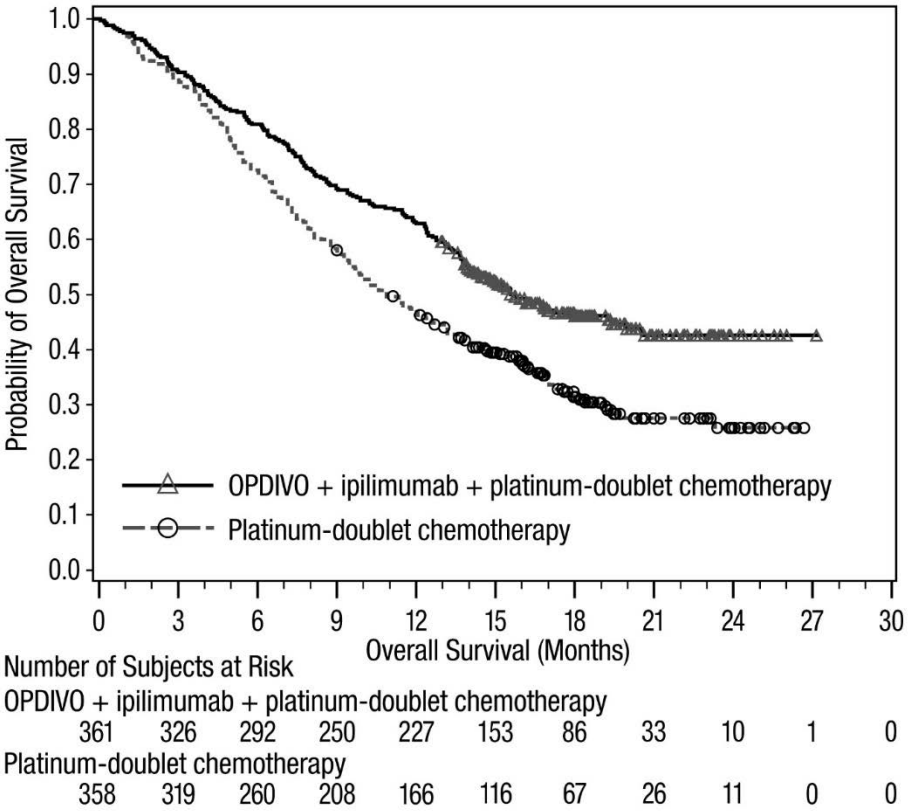
[d] Kaplan-Meier estimate.

[e] Confidence interval based on the Clopper and Pearson Method.

[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving OPDIVO and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 9).

Figure 9: Overall Survival - CHECKMATE-9LA



Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-017 (NCT01642004) was a randomized (1:1), open-label trial in 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=135) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=137). Randomization was stratified by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This trial included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS.

The trial population characteristics were: median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were White (93%) and male (76%); the majority of patients were enrolled in Europe (57%) with the remainder in US/Canada (32%) and the rest of the world (11%). Baseline ECOG performance status was 0 (24%) or 1 (76%) and 92% were former/current smokers. Baseline disease characteristics of the population as

reported by investigators were Stage IIIb (19%), Stage IV (80%), and brain metastases (6%). All patients received prior therapy with a platinum-doublet regimen and 99% of patients had tumors of squamous-cell histology.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Efficacy results are shown in Table 64 and Figure 10.

Table 64: Efficacy Results - CHECKMATE-017

	OPDIVO (n=135)	**Docetaxel (n=137)**
Overall Survival		
Deaths (%)	86 (64%)	113 (82%)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Hazard ratio (95% CI)[a]	0.59 (0.44, 0.79)	
p-value[b,c]	0.0002	
Overall Response Rate	27 (20%)	12 (9%)
(95% CI)	(14, 28)	(5, 15)
p-value[d]	0.0083	
Complete response	1 (0.7%)	0
Median duration of response (months) (95% CI)	NR[e] (9.8, NR[e])	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

[a] Based on a stratified proportional hazards model.

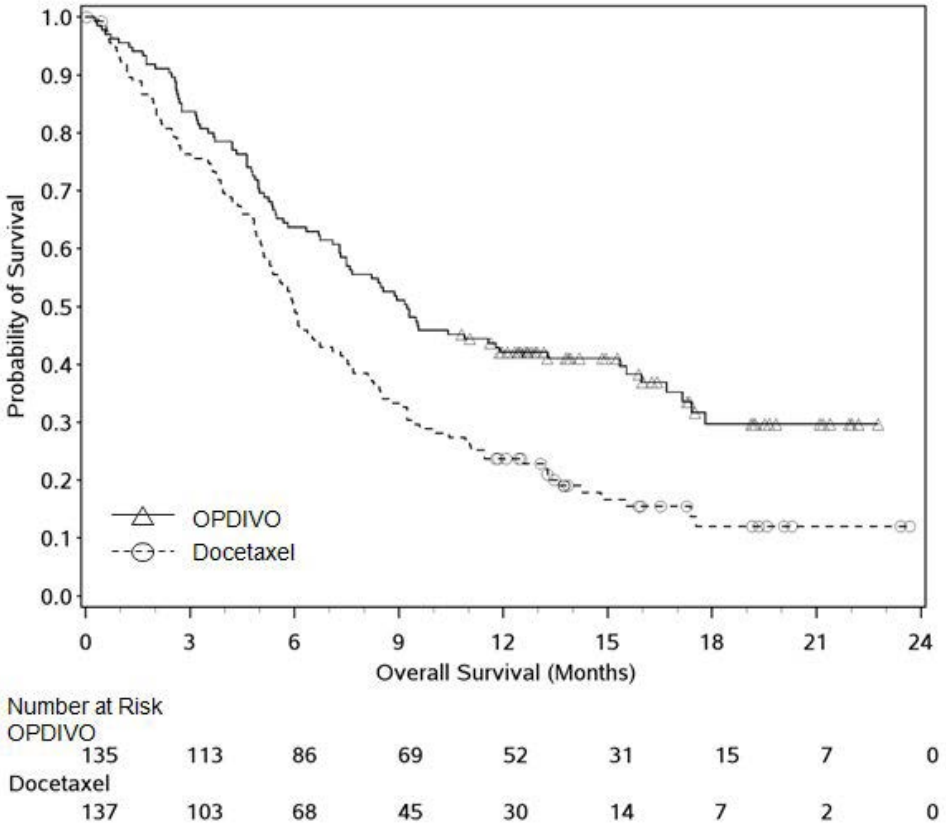
[b] Based on stratified log-rank test.

[c] p-value is compared with 0.0315 of the allocated alpha for this interim analysis.

[d] Based on the stratified Cochran-Mantel-Haenszel test.

[e] Not Reached.

Figure 10: Overall Survival - CHECKMATE-017



Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the trial population, 17% of 272 patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1 and 53% had PD-L1 positive squamous NSCLC defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive subgroup.

Second-line Treatment of Metastatic Non-Squamous NSCLC

CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=292) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=290). Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional

efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (92%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%).

CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 65 and Figure 11.

Table 65: Efficacy Results - CHECKMATE-057

	OPDIVO (n=292)	**Docetaxel (n=290)**
Overall Survival		
Deaths (%)	190 (65%)	223 (77%)
Median (months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.0, 10.7)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0015	
Overall Response Rate	56 (19%)	36 (12%)
(95% CI)	(15, 24)	(9, 17)
p-value[d]	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Median duration of response (months) (95% CI)	17 (8.4, NR[e])	6 (4.4, 7.0)
Progression-free Survival		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI)[a]	0.92 (0.77, 1.11)	
p-value[b]	0.39	

[a] Based on a stratified proportional hazards model.

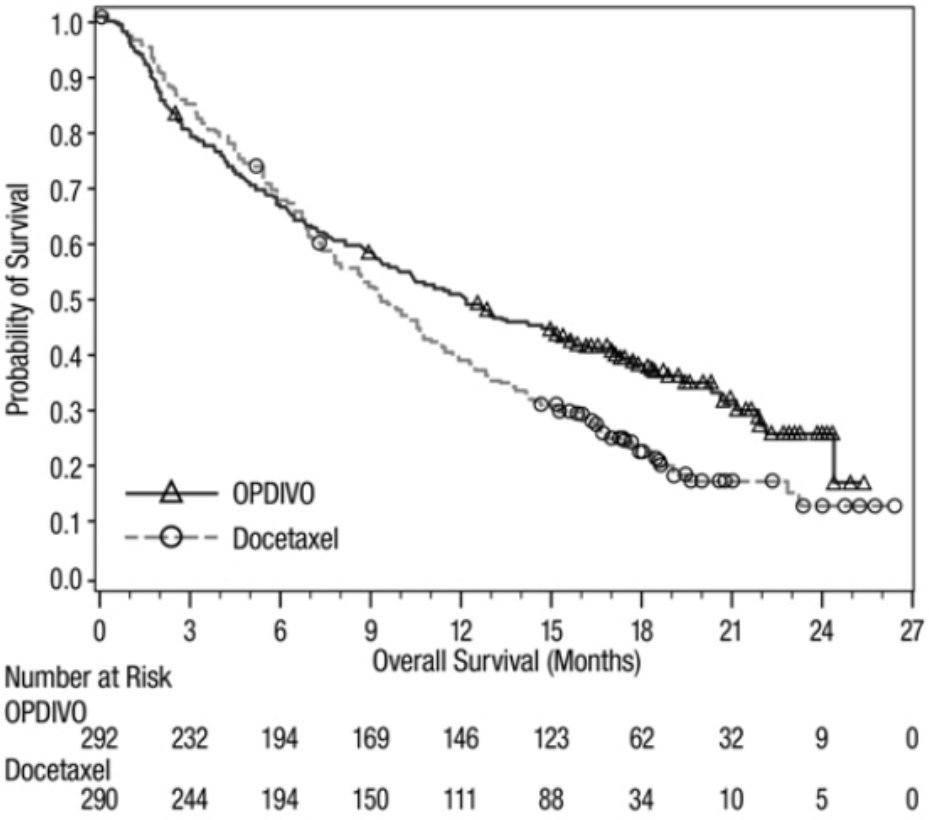
[b] Based on stratified log-rank test.

[c] p-value is compared with .0408 of the allocated alpha for this interim analysis.

[d] Based on the stratified Cochran-Mantel-Haenszel test.

[e] Not Reached.

Figure 11: Overall Survival - CHECKMATE-057



Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the trial population, 22% of 582 patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% had ≥1% but <5% tumor cells with positive staining, 7% had ≥5% but <10% tumor cells with positive staining, and 67% had ≥10% tumor cells with positive staining. Figures 12 and 13 summarize the results of prespecified analyses of OS and PFS in subgroups determined by percentage of tumor cells expressing PD-L1.

Figure 12: Forest Plot: OS Based on PD-L1 Expression - CHECKMATE-057

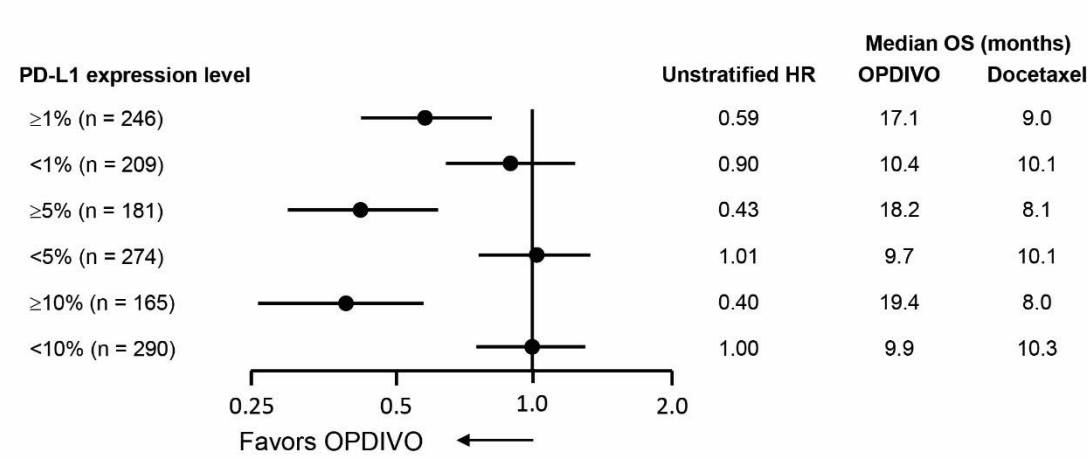
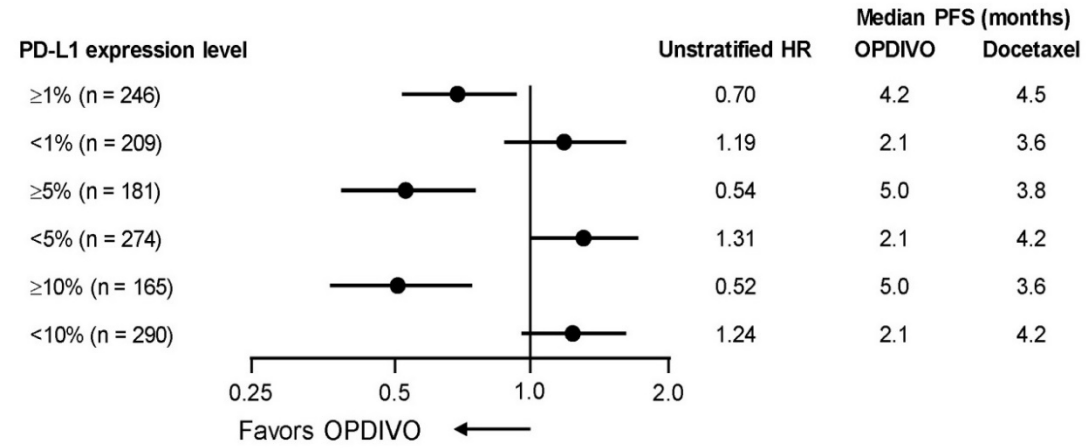


Figure 13: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.6 Malignant Pleural Mesothelioma

CHECKMATE-743 (NCT02899299) was a randomized, open-label trial in patients with unresectable malignant pleural mesothelioma. The trial included patients with histologically confirmed and previously untreated malignant pleural mesothelioma with no palliative radiotherapy within 14 days of initiation of therapy. Patients with interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, or active brain metastasis were excluded from the trial.

Patients were randomized 1:1 to receive either:

- OPDIVO 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years, or
- cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2, or carboplatin 5 AUC and pemetrexed 500 mg/m^2 administered every 3 weeks for 6 cycles.

Stratification factors for randomization were tumor histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and sex (male vs. female). Study treatment continued for up to 2 years, or until disease progression or unacceptable toxicity. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR utilizing modified RECIST criteria.

A total of 605 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89), with 72% of patients ≥65 years and 26% ≥75 years; 85% were White, 11% were Asian, and 77% were male. Baseline ECOG performance status was 0 (40%) or 1 (60%), 35% had Stage III and 51% had Stage IV disease, 75% had epithelioid and 25% had non-epithelioid histology, 75% had tumors with PD-L1 expression ≥1%, and 22% had tumors with PD-L1 expression <1%.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO in combination with ipilimumab compared to chemotherapy. Efficacy results from the prespecified interim analysis are presented in Table 66 and Figure 14.

Table 66: Efficacy Results - CHECKMATE-743

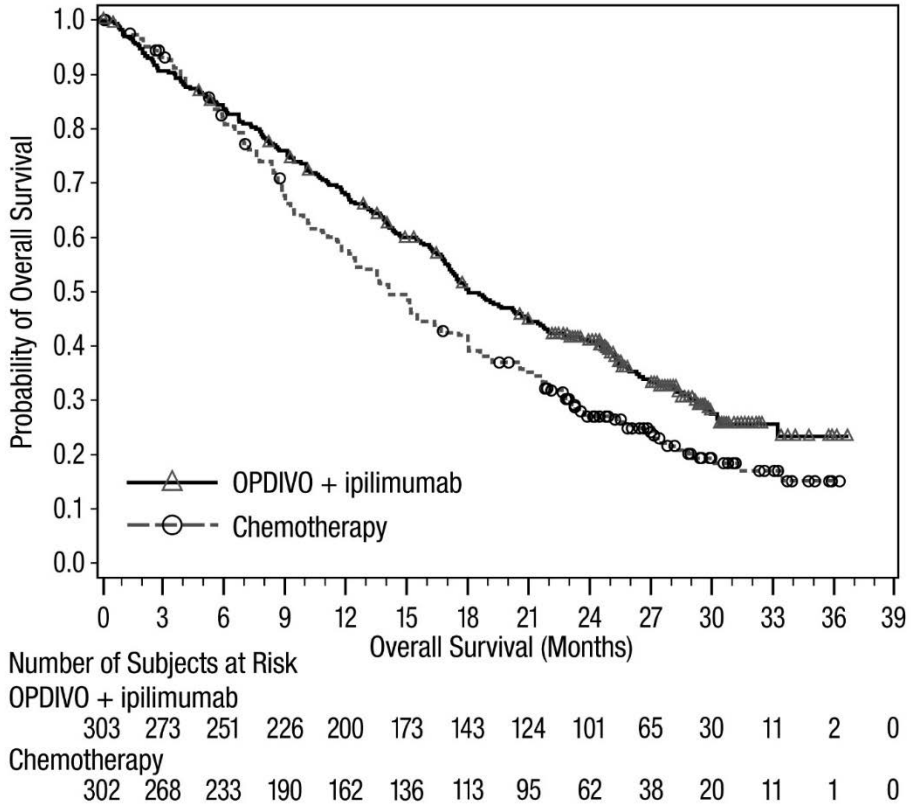
	OPDIVO and Ipilimumab (n=303)	**Chemotherapy (n=302)**
Overall Survival[a]		
Events (%)	200 (66)	219 (73)
Median (months)[b] (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Hazard ratio (95% CI)[c]	0.74 (0.61, 0.89)	
Stratified log-rank p-value[d]	0.002	
Progression-free Survival		
Events (%)	218 (72)	209 (69)
Hazard ratio (95% CI)[c]	1.0 (0.82, 1.21)	
Median (months)[b] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate[e]	40%	43%
(95% CI)	(34, 45)	(37, 49)
Duration of Response		

Table 66: Efficacy Results - CHECKMATE-743

	OPDIVO and Ipilimumab (n=303)	Chemotherapy (n=302)
Median (months)[b] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)

[a] At the time of the interim analysis, 419 deaths (89% of the deaths needed for the final analysis) had occurred.
[b] Kaplan-Meier estimate.
[c] Stratified Cox proportional hazard model.
[d] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.
[e] Based on confirmed response by BICR.

Figure 14: Overall Survival - CHECKMATE-743



In a prespecified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology, the hazard ratio (HR) for OS was 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the OPDIVO and ipilimumab arm and 16.2 months in the chemotherapy arm. In the subgroup of patients with non-epithelioid histology, the HR for OS was 0.46 (95% CI: 0.31, 0.70), with median OS of 16.9 months in the OPDIVO and ipilimumab arm and 8.8 months in the chemotherapy arm.

14.7 Advanced Renal Cell Carcinoma

First-line Renal Cell Carcinoma

CHECKMATE-214

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label trial in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of >10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg intravenously every two weeks (n=425), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=422). Treatment continued until disease progression or unacceptable toxicity.

The trial population characteristics were: median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO and ipilimumab as compared with sunitinib (Table 67 and Figure 15). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. Efficacy results are shown in Table 67 and Figure 15.

Table 67: Efficacy Results - CHECKMATE-214

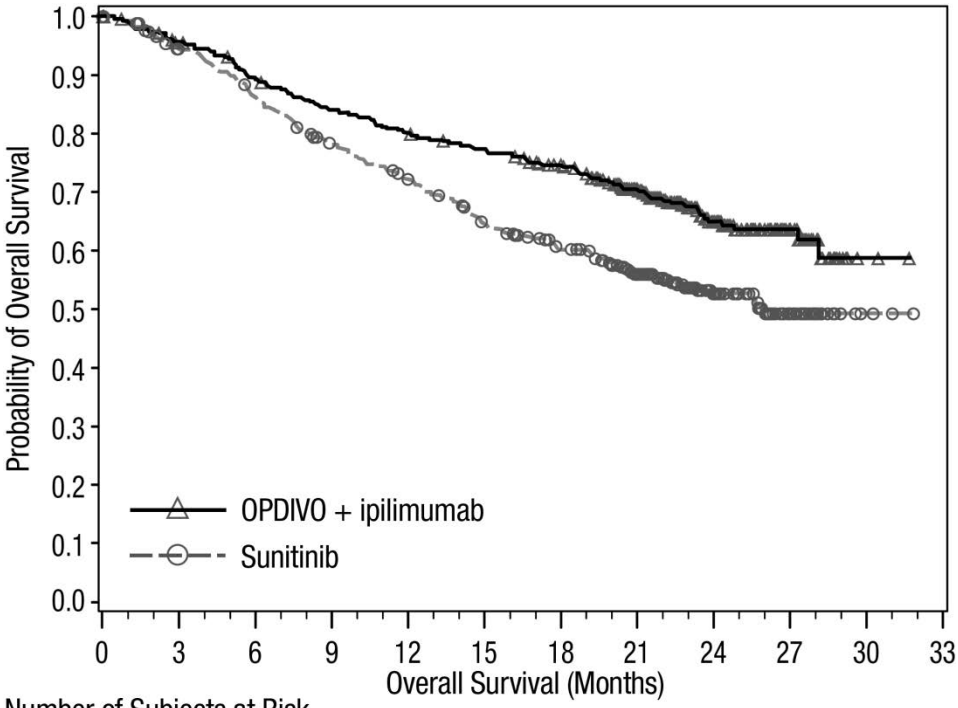
	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NR[a]	25.9
Hazard ratio (99.8% CI)[b]	0.63 (0.44, 0.89)	
p-value[c,d]	<0.0001	

Table 67: Efficacy Results - CHECKMATE-214

	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Confirmed Overall Response Rate (95% CI)	41.6% (36.9, 46.5)	26.5% (22.4, 31.0)
p-value[e,f]	<0.0001	
Complete response (CR)	40 (9.4)	5 (1.2)
Partial response (PR)	137 (32.2)	107 (25.4)
Median duration of response (months) (95% CI)	NR[a] (21.8, NR[a])	18.2 (14.8, NR[a])
Progression-free Survival		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[c]	NS[g]	

[a] Not Reached.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[e] Based on the stratified DerSimonian-Laird test.
[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[g] Not Significant at alpha level of 0.009.

Figure 15: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214



Number of Subjects at Risk

OPDIVO + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to OPDIVO and ipilimumab (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving OPDIVO and ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of OPDIVO and ipilimumab in previously untreated renal cell carcinoma with favorable-risk disease has not been established.

CHECKMATE-9ER

CHECKMATE-9ER (NCT03141177) was a randomized, open-label study of OPDIVO combined with cabozantinib versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression (≥1% vs. <1% or indeterminate), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World).

Patients were randomized to OPDIVO 240 mg intravenously every 2 weeks and cabozantinib 40 mg orally daily (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Treatment continued until disease progression per RECIST v1.1 or unacceptable toxicity. Treatment beyond

RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 28 to 90) with 38% ≥65 years of age and 10% ≥75 years of age. The majority of patients were male (74%) and White (82%) and 23% and 77% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. Patient distribution by IMDC risk categories was 22% favorable, 58% intermediate, and 20% poor.

The major efficacy outcome measure was PFS (BICR assessed). Additional efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to OPDIVO and cabozantinib compared with sunitinib. Consistent results for PFS were observed across pre-specified subgroups of IMDC risk categories and PD-L1 tumor expression status. An updated OS analysis was conducted when 271 deaths were observed based on the pre-specified number of deaths for the pre-planned final analysis of OS. Efficacy results are shown in Table 68 and Figures 16 and 17.

Table 68: Efficacy Results - CHECKMATE-9ER

	OPDIVO and Cabozantinib (n=323)	**Sunitinib (n=328)**
Progression-free Survival		
Disease progression or death (%)	144 (45)	191 (58)
Median PFS (months)[a] (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI)[b]	0.51 (0.41, 0.64)	
p-value[c,d]	<0.0001	
Overall Survival		
Deaths (%)	67 (21)	99 (30)
Median OS (months)[a] (95% CI)	NR[e]	NR (22.6, NR[e])
Hazard ratio (98.89% CI)[b]	0.60 (0.40, 0.89)	
p-value[c,d,f]	0.0010	
Updated Overall Survival		
Deaths (%)	121 (37)	150 (46)
Median OS (months)[a] (95% CI)	37.7 (35.5, NR)	34.3 (29.0, NR)
Hazard ratio (95% CI)[b]	0.70 (0.55, 0.90)	
Confirmed Objective Response Rate (95% CI)[g]	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value[h]	<0.0001	

Table 68: Efficacy Results - CHECKMATE-9ER

	OPDIVO and Cabozantinib (n=323)	Sunitinib (n=328)
Complete Response	26 (8%)	15 (4.6%)
Partial Response	154 (48%)	74 (23%)
Median duration of response in months (95% CI)[a]	20.2 (17.3, NR[e])	11.5 (8.3, 18.4)

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model.
[c] Based on stratified log-rank test.
[d] 2-sided p-values from stratified log-rank test.
[e] Not Reached.
[f] p-value is compared with the allocated alpha of 0.0111 for this interim analysis.
[g] CI based on the Clopper-Pearson method.
[h] 2-sided p-value from Cochran-Mantel-Haenszel test.

Figure 16: Progression-free Survival - CHECKMATE-9ER

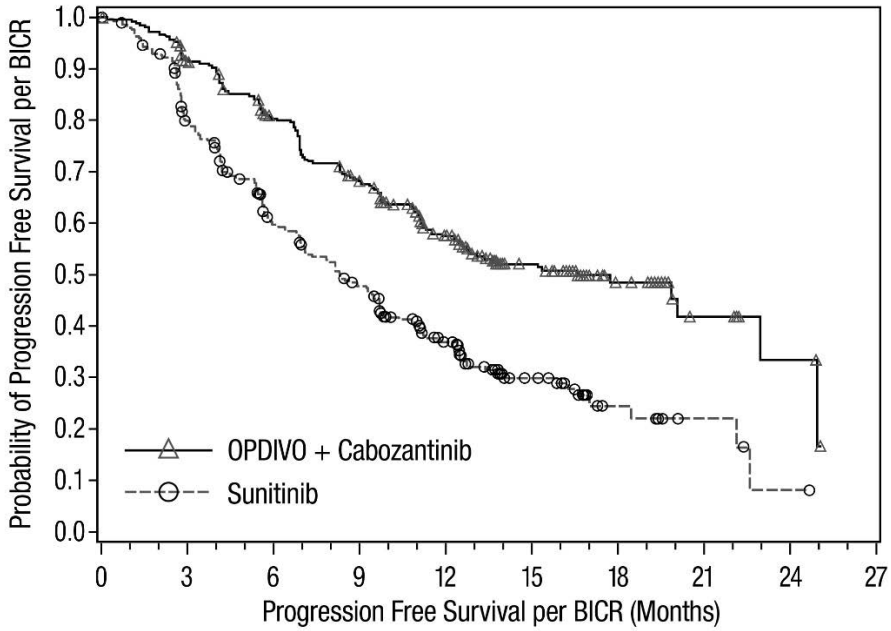
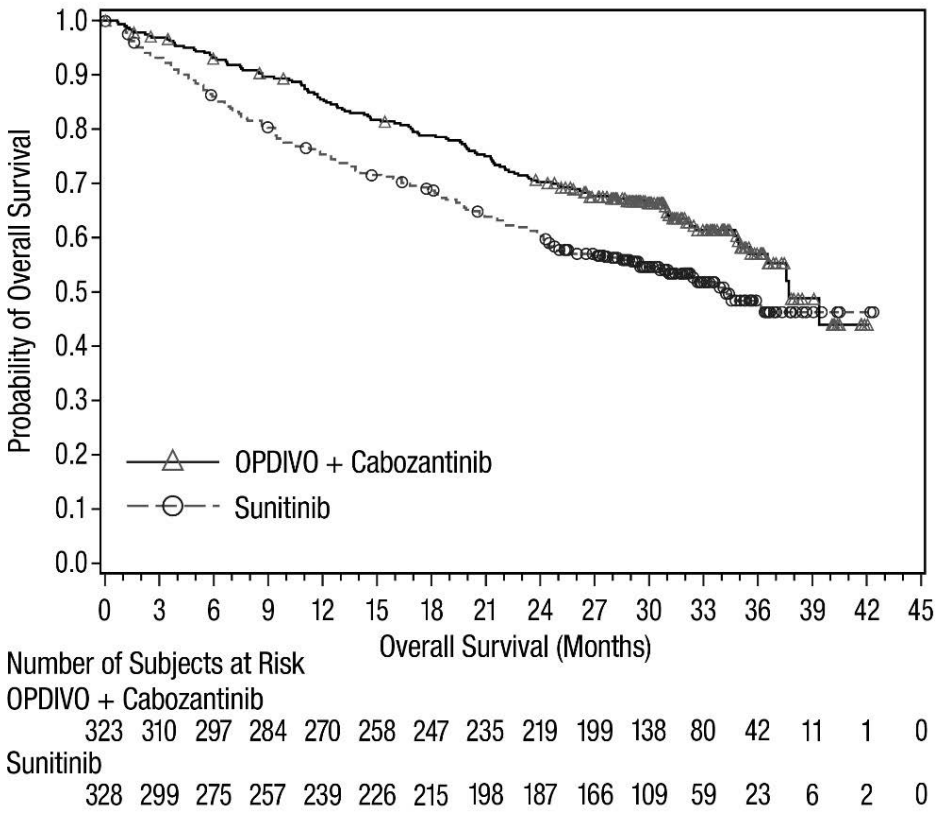


Figure 17: Updated Overall Survival - CHECKMATE-9ER



In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR (95% CI) of 1.03 (0.55, 1.92), 0.74 (0.54, 1.01), 0.65 (0.50, 0.85), and 0.49 (0.31, 0.79), respectively.

Previously Treated Renal Cell Carcinoma

CHECKMATE-025

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label trial in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. The trial excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies. Patients were randomized OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=410) or everolimus 10 mg orally daily (n=411). The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. The major efficacy outcome measure was overall survival (OS).

The trial population characteristics were: median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and White (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis). OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 69 and Figure 18.

Table 69: Efficacy Results - CHECKMATE-025

	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival (months) (95% CI)	25.0 (21.7, NR[a])	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[b]	0.73 (0.60, 0.89)	
p-value[c,d]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response (months) (95% CI)	23.0 (12.0, NR[a])	13.7 (8.3, 21.9)
Median time to onset of confirmed response (months) (min, max)	3.0 (1.4, 13.0)	3.7 (1.5, 11.2)

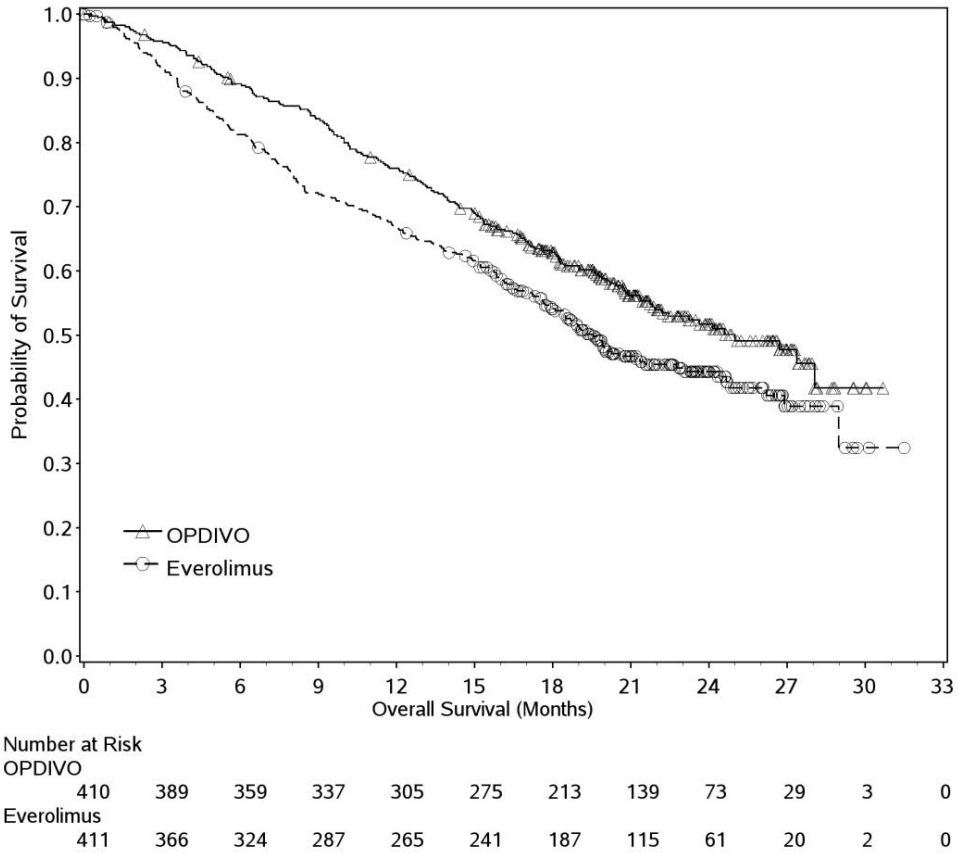
[a] Not Reached.

[b] Based on a stratified proportional hazards model.

[c] Based on a stratified log-rank test.

[d] p-value is compared with 0.0148 of the allocated alpha for this interim analysis.

Figure 18: Overall Survival - CHECKMATE-025



Number at Risk

OPDIVO	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

14.8 Classical Hodgkin Lymphoma

Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT.

CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance <40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity.

Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

Efficacy was evaluated by ORR as determined by an IRRC. Additional outcome measures included duration of response (DOR).

Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and White (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Efficacy results are shown in Table 70.

Table 70: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

	CHECKMATE-205 and CHECKMATE-039 (n=95)
Overall Response Rate, n (%)[a] (95% CI)	63 (66%) (56, 76)
Complete remission rate (95% CI)	6 (6%) (2, 13)
Partial remission rate (95% CI)	57 (60%) (49, 70)
Duration of Response (months)	
Median[b] (95% CI)	13.1 (9.5, NR[d])
Range[c]	0+, 23.1+
Time to Response (months)	
Median	2.0
Range	0.7, 11.1

[a] Per 2007 revised International Working Group criteria.

[b] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 9.9 months.

[c] A + sign indicates a censored value.

[d] Not Reached.

Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after autologous HSCT. The analysis included the group described above. The median age was 34 years (range: 18 to 72). The majority were male (59%) and White (86%). Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab vedotin, 17% received it only before autologous HSCT, 78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Efficacy results are shown in Table 71.

Table 71: Efficacy in cHL after Autologous HSCT

	CHECKMATE-205 and CHECKMATE-039 (n=258)
Overall Response Rate, n (%)	179 (69%)
(95% CI)	(63, 75)
Complete remission rate	37 (14%)
(95% CI)	(10, 19)
Partial remission rate	142 (55%)
(95% CI)	(49, 61)
Duration of Response (months)	
Median[a, b]	NR[c]
(95% CI)	(12.0, NR[c])
Range	0+, 23.1+
Time to Response (months)	
Median	2.0
Range	0.7, 11.1

[a] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.

[b] The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.

[c] Not Reached.

14.9 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label trial enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or investigator's choice of cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously weekly).

Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR.

A total of 361 patients were randomized; 240 patients to the OPDIVO arm and 121 patients to the investigator's choice arm (docetaxel: 45%; methotrexate: 43%; and cetuximab: 12%). The trial population characteristics were: median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male. Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 45% of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy, and 25% had HPVp16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs. 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively). Efficacy results are shown in Table 72 and Figure 19.

Table 72: Overall Survival - CHECKMATE-141

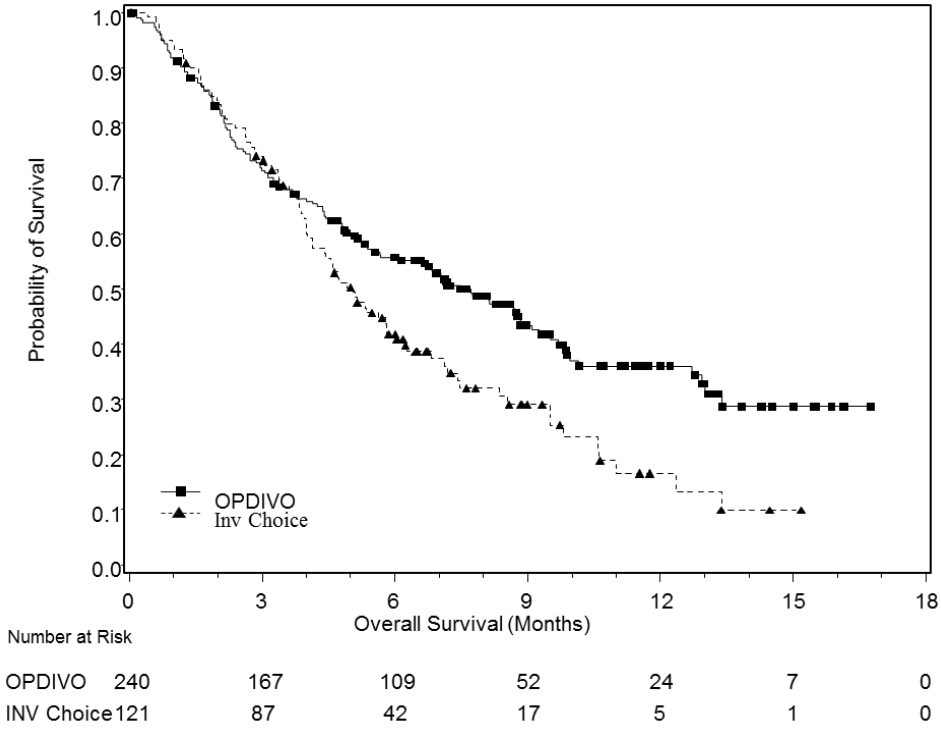
	OPDIVO (n=240)	**Cetuximab, Methotrexate or Docetaxel (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[a] Based on stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with 0.0227 of the allocated alpha for this interim analysis.

Figure 19: Overall Survival - CHECKMATE-141



Number at Risk

OPDIVO	240	167	109	52	24	7	0
INV Choice	121	87	42	17	5	1	0

Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the trial population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup.

14.10 Urothelial Carcinoma

Adjuvant Treatment of UC at High Risk of Recurrence

CHECKMATE-274 (NCT02632409) was a randomized, double-blind, placebo-controlled study of adjuvant OPDIVO in patients who were within 120 days of radical resection (R0) of UC of the bladder or upper urinary tract (renal pelvis or ureter) at high risk of recurrence. High risk of recurrence was defined as either 1) ypT2-ypT4a or ypN^+ for patients who received neoadjuvant cisplatin or 2) pT3-pT4a or pN^+ for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin. Patients were randomized 1:1 to receive OPDIVO 240 mg or placebo by intravenous infusion every 2 weeks until recurrence or until unacceptable toxicity for a maximum treatment duration of 1 year. Patients were stratified by pathologic nodal status (N+ vs. N0/x with <10 nodes removed vs. N0 with ≥10 nodes removed),

tumor cells expressing PD-L1 (≥1% vs. <1%/indeterminate as determined by the central lab using the PD-L1 IHC 28-8 pharmDx assay), and use of neoadjuvant cisplatin (yes vs. no).

The trial population characteristics were: median age of 67 years (range: 30 to 92); 76% male; 76% White, 22% Asian, 0.7% Black, and 0.1% American Indian or Alaska Native. Of the 335 (47%) of patients with node-positive UC, 44 (6%) had non–muscle-invasive (<pT2) primary tumors. ECOG performance status was 0 (63%), 1 (35%), or 2 (2%). Prior neoadjuvant cisplatin had been given to 43% of patients; of the 57% who did not receive prior neoadjuvant cisplatin, reasons listed were ineligibility (22%), patient preference (33%), and other/not reported (2%). Tumor PD-L1 expression was ≥1% in 40% of patients, and 21% of patients had upper tract UC.

The major efficacy outcome measures were investigator-assessed DFS in all randomized patients and in patients with tumors expressing PD-L1 ≥1%. DFS was defined as time to first recurrence (local urothelial tract, local non-urothelial tract, or distant metastasis), or death. Additional efficacy outcome measures included OS.

At the pre-specified interim analysis, CHECKMATE-274 demonstrated a statistically significant improvement in DFS for patients randomized to OPDIVO vs. placebo in the all randomized patient population, as well as in the subpopulation of patients with PD-L1 ≥1%, as shown in Table 73 and Figure 20.

In exploratory subgroup analyses in patients with upper tract UC (n=149), no improvement in DFS was observed in the nivolumab arm compared to the placebo arm. The unstratified DFS hazard ratio estimate was 1.15 (95% CI: 0.74, 1.80).

In an exploratory subgroup analysis in patients with PD-L1 expression of <1% (n=414), the unstratified DFS hazard ratio estimate was 0.83 (95% CI: 0.64, 1.08).

OS data is immature with 33% of deaths in the overall randomized population. In the UTUC subpopulation, 37 deaths occurred (20 in the nivolumab arm, 17 in the placebo arm).

Table 73: Efficacy Results - CHECKMATE-274

	All Randomized		**PD-L1 ≥1%**	
	OPDIVO (n=353)	**Placebo (n=356)**	**OPDIVO (n=140)**	**Placebo (n=142)**
Disease-free Survival				
Events[a], n (%)	170 (48)	204 (57)	55 (39)	81 (57)
Local recurrence	47 (13)	64 (18)	10 (7)	24 (17)
Distant recurrence	108 (31)	127 (36)	40 (29)	52 (37)
Death	14 (4)	10 (3)	5 (4)	5 (4)
Median DFS (months)[b]	20.8	10.8	N.R.	8.4
(95% CI)	(16.5, 27.6)	(8.3, 13.9)	(21.2, N.E.)	(5.6, 21.2)
Hazard ratio[c]	0.70		0.55	
(95% CI)	(0.57, 0.86)		(0.39, 0.77)	

Table 73: Efficacy Results - CHECKMATE-274

	All Randomized		PD-L1 ≥1%	
	OPDIVO (n=353)	**Placebo (n=356)**	**OPDIVO (n=140)**	**Placebo (n=142)**
Disease-free Survival				
p-value	0.0008[d]		0.0005[e]	

N.R. Not Reached, N.E. Not Estimable

[a] Includes disease at baseline events (protocol deviations): n=1 in OPDIVO arm and n=3 in placebo arm.

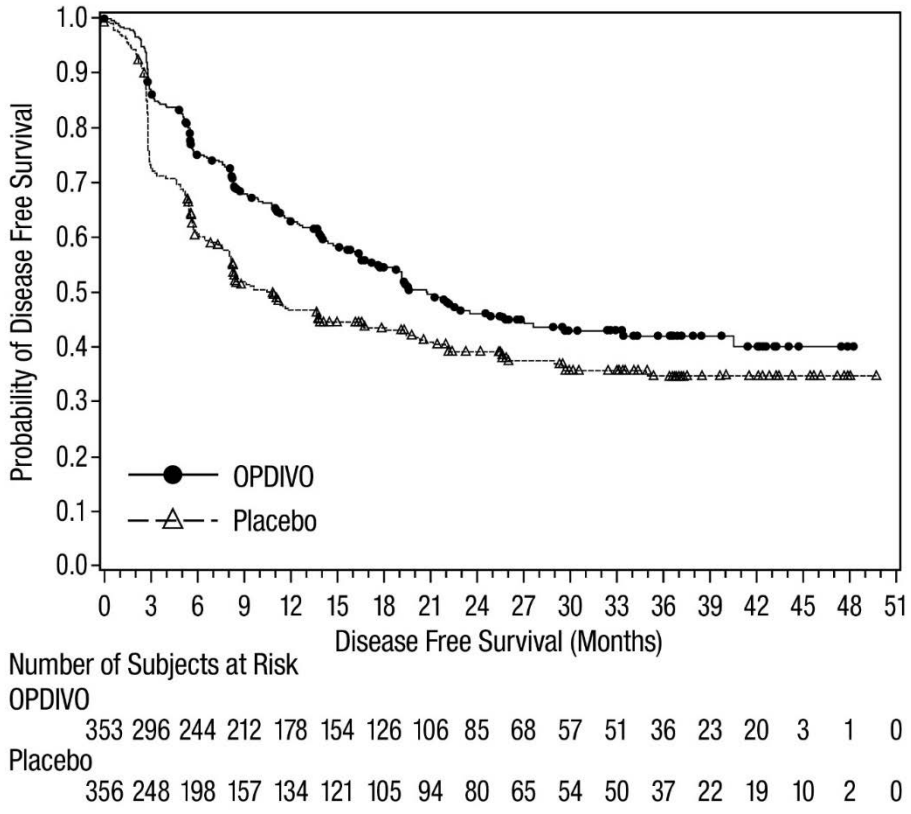
[b] Based on Kaplan-Meier estimates.

[c] Stratified Cox proportional hazard model. Hazard ratio is OPDIVO over placebo.

[d] Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status, PD-L1 status (≥1% vs <1%/indeterminate). Boundary for statistical significance in all randomized patients: p-value <0.01784.

[e] Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status. Boundary for statistical significance in all randomized patients with PD-L1 ≥1%: p-value <0.01282.

Figure 20: Disease-free Survival in All Randomized Patients - CHECKMATE-274



First-line Treatment of Unresectable or Metastatic UC

CHECKMATE-901 (NCT 03036098) was a randomized, open-label study in patients with previously untreated unresectable or metastatic UC. Prior neoadjuvant or adjuvant chemotherapy

were permitted as long as the disease recurrence took place ≥12 months from completion of therapy. Patients who were ineligible for cisplatin and those with active CNS metastases were excluded. Stratification factors for randomization were PD-L1 status (≥1% vs. <1% or indeterminate) and liver metastasis. Patients were randomized 1:1 to receive either:

- OPDIVO 360 mg and cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle of a 21-day cycle for up to 6 cycles followed by single-agent OPDIVO 480 mg every 4 weeks until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, OPDIVO was continued for up to 2 years from first dose.
- Cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle for up to 6 cycles, until disease progression or unacceptable toxicity.

The major efficacy outcome measures were OS and PFS as assessed by BICR using RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.

The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥65 years of age and 12% of patients ≥75 years of age, 23% were Asian, 72% were White, 0.3% were Black, 0.3% were American Indian or Alaska Native, 4.9% were Other, 12% were Hispanic or Latino, and 77% were male. Baseline ECOG performance status was 0 (53%) or 1 (46%). At baseline, 87% of patients had metastatic UC, including 20% with liver metastases, 11% had locally advanced UC, and 51% had UC histologic variants. Forty-nine (16%) in the OPDIVO in combination with cisplatin-based chemotherapy arm and 43 (14%) in the cisplatin-based chemotherapy arm switched from cisplatin to carboplatin after at least one cycle of cisplatin.

Efficacy results are presented in Table 74 and Figures 21 and 22.

Table 74: Efficacy Results – CHECKMATE 901

	OPDIVO and Cisplatin and Gemcitabine (n=304)	**Cisplatin and Gemcitabine (n=304)**
Overall Survival (OS)		
Events, n (%)	172 (56.6)	193 (63.5)
Median (months) (95% CI)[a]	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival (PFS)[d]		
Events, n (%)	211 (69.4)	191 (62.8)
Median (months) (95% CI)[a]	7.9 (7.6, 9.5)	7.6 (6.0, 7.8)

Table 74: Efficacy Results – CHECKMATE 901

	OPDIVO and Cisplatin and Gemcitabine (n=304)	**Cisplatin and Gemcitabine (n=304)**
Hazard ratio (95% CI)[b]	0.72 (0.59, 0.88)	
p-value[c]	0.0012	
Objective Response Rate (ORR)[d]		
Response rate, n (%) (95% CI)	175 (57.6%) (51.8, 63.2)	131 (43.1%) (37.5, 48.9)
Complete response rate, n (%)	66 (22%)	36 (12%)
Partial response rate, n (%)	109 (36%)	95 (31%)
Duration of Response (DoR)		
Median (months) (95% CI)[a]	9.5 (7.6, 15.1)	7.3 (5.7, 8.9)

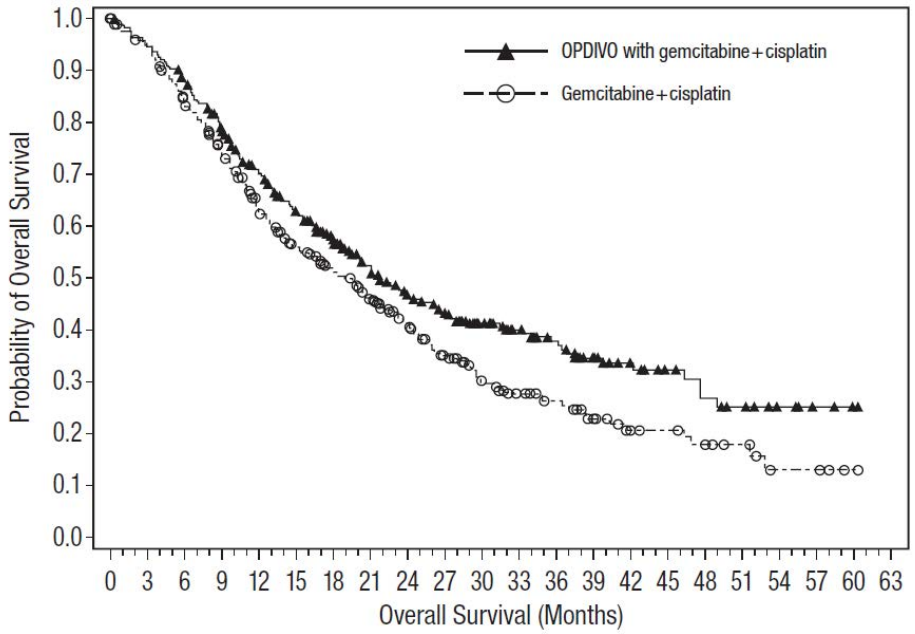
[a] Based on Kaplan-Meier Estimates.

[b] Stratified Cox proportional hazard model.

[c] 2 sided p values from stratified log-rank test.

[d] Assessed by BICR.

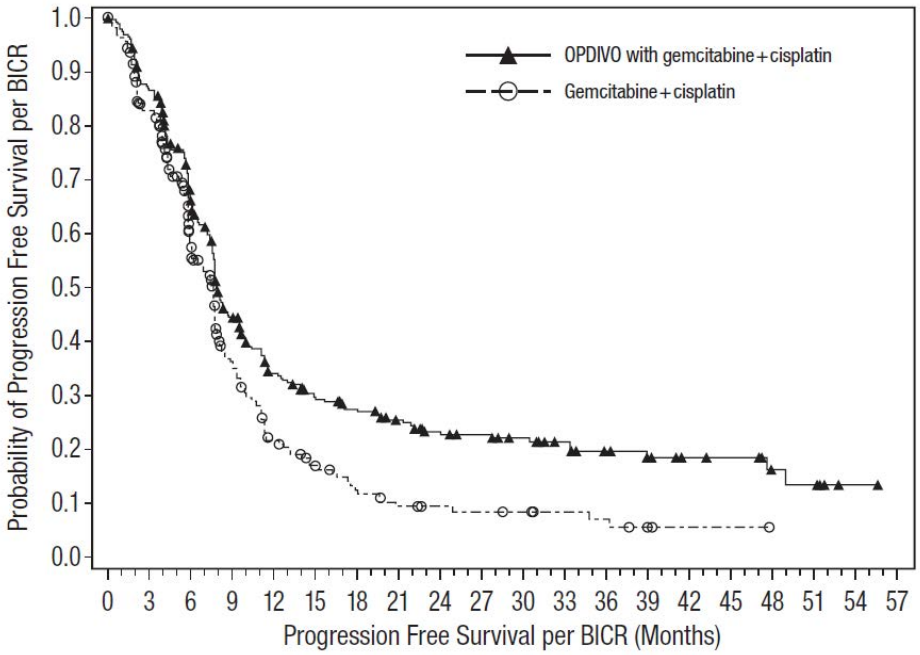
Figure 21: Overall Survival - CHECKMATE-901



Number of Subjects at Risk

OPDIVO with gemcitabine + cisplatin	304	286	264	228	196	167	142	119	97	84	69	58	48	36	25	20	15	12	7	4	2	0
Gemcitabine + cisplatin	304	277	242	208	166	140	122	102	82	65	49	39	33	24	17	16	13	9	4	4	1	0

Figure 22: Progression-free Survival - CHECKMATE-901



Previously Treated Advanced or Metastatic UC

CHECKMATE-275 (NCT02387996) was a single-arm trial in 270 patients with locally advanced or metastatic UC who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRRC using RECIST v1.1 and DOR.

The median age was 66 years (range: 38 to 90), 78% were male, 86% were White. Twenty-seven percent had non-bladder urothelial carcinoma and 84% had visceral metastases. Thirty-four percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy. Twenty-nine percent of patients had received ≥2 prior systemic regimens in the metastatic setting. Thirty-six percent of patients received prior cisplatin only, 23% received prior carboplatin only, and 7% were treated with both cisplatin and carboplatin in the metastatic setting. Forty-six percent of patients had an ECOG performance status of 1. Eighteen percent of patients

had a hemoglobin <10 g/dL, and twenty-eight percent of patients had liver metastases at baseline. Patients were included regardless of their PD-L1 status.

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are shown in Table 75. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 75: Efficacy Results - CHECKMATE-275

	All Patients N=270	**PD-L1 <1% N=146**	**PD-L1 ≥1% N=124**
Confirmed Overall Response Rate, n (%) (95% CI)	53 (19.6%) (15.1, 24.9)	22 (15.1%) (9.7, 21.9)	31 (25.0%) (17.7, 33.6)
Complete response rate	7 (2.6%)	1 (0.7%)	6 (4.8%)
Partial response rate	46 (17.0%)	21 (14.4%)	25 (20.2%)
Median Duration of Response[a] (months) (range)	10.3 (1.9+, 12.0+)	7.6 (3.7, 12.0+)	NR[b] (1.9+, 12.0+)

[a] Estimated from the Kaplan-Meier Curve.

[b] Not Reached.

14.11 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

Treatment of MSI-H or dMMR mCRC In Combination with Ipilimumab

CHECKMATE-8HW (NCT03143153) was a randomized, 3-arm, open-label trial in immunotherapy-naive patients across all lines of therapy with unresectable or metastatic CRC with known tumor MSI-H or dMMR (MSI-H/dMMR) status as determined in accordance with local standard of practice using PCR, NGS, or IHC assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumor specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary study population.

The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors.

Patients were randomized to receive one of the following treatments:

- OPDIVO 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then OPDIVO 480 mg every 4 weeks.

- OPDIVO 240 mg every 2 weeks for 6 doses, then OPDIVO 480 mg every 4 weeks.
- Investigator's choice chemotherapy
  - mFOLFOX6 (oxaliplatin, leucovorin, and FU) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus followed by FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks.
  - FOLFIRI (irinotecan, leucovorin, and FU) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus and FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks.

Randomization was stratified by tumor location (right vs left) and by prior lines of therapy (0, 1, 2L+). Patients randomized to the chemotherapy arm could receive OPDIVO in combination with ipilimumab upon progression assessed by BICR.

Study treatment was administered until disease progression, unacceptable toxicity, or for up to 2 years for patients who received OPDIVO plus ipilimumab or nivolumab monotherapy. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. OPDIVO with or without ipilimumab could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumor assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter up until week 96, then every 16 weeks thereafter up until week 144, and then every 24 weeks.

The evaluation of efficacy relied on the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to OPDIVO in combination with ipilimumab versus chemotherapy in the first-line (1L) setting and the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to OPDIVO plus ipilimumab vs nivolumab in all lines setting.

The major efficacy outcome measure was BICR-assessed PFS per RECIST 1.1. Additional efficacy outcome measures included ORR and duration of response assessed by BICR and OS.

The baseline characteristics of the total of 839 patients randomized were: the median age was 63 years (range: 20 to 87), with 46% ≥65 years of age and 14% ≥75 years of age; 50% were male and 87% were White, 9.3% were Asian, 1.5% Black or African American, and 2.3% other race; 9.2% were Hispanic or Latino, 50% Not Hispanic or Latino, 41% ethnicity unknown. Baseline ECOG performance status was 0 (52%) and 1 (48%); number of prior lines of therapy was 0 (56%), 1 (24%), and ≥2 (19%); and tumor location was right-sided or left-sided for 69% and 31% of patients. The baseline characteristics in patients with centrally confirmed MSI-H/dMMR is consistent with that of all randomized patients.

First Line OPDIVO in combination with ipilimumab

Among 303 patients in the first-line setting who were randomly assigned to OPDIVO in combination with ipilimumab (202) and to chemotherapy (101), 171 and 84 patients had centrally

confirmed MSI-H/dMMR status in OPDIVO in combination with ipilimumab arm and chemotherapy arm, respectively.

In the 1L setting 200 of 202 patients assigned to receive OPDIVO combined with ipilimumab and 88 of 101 patients assigned to receive chemotherapy received at least 1 dose of study treatment. Among the 88 patients who received chemotherapy, 58% and 42% of patients received oxaliplatin-containing regimens and irinotecan-containing regimens, respectively, and 66 (75%) patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

The BICR-assessed PFS efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the OPDIVO and ipilimumab arm compared with chemotherapy in the 1L setting are presented in Table 76 and Figure 23. The comparative results of ORR and OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 76: Efficacy Results, First Line - CHECKMATE-8HW

	OPDIVO and Ipilimumab (n=171)	**Chemotherapy (n=84)**
Progression-free Survival		
Disease progression or death (%)	48 (28)	52 (62)
Median in months[b] (95% CI)	NR (38.4, NE)	5.8 (4.4, 7.8)
Hazard ratio[c] (95% CI)	0.21 (0.14, 0.32)	
p-value[a]	<0.0001	

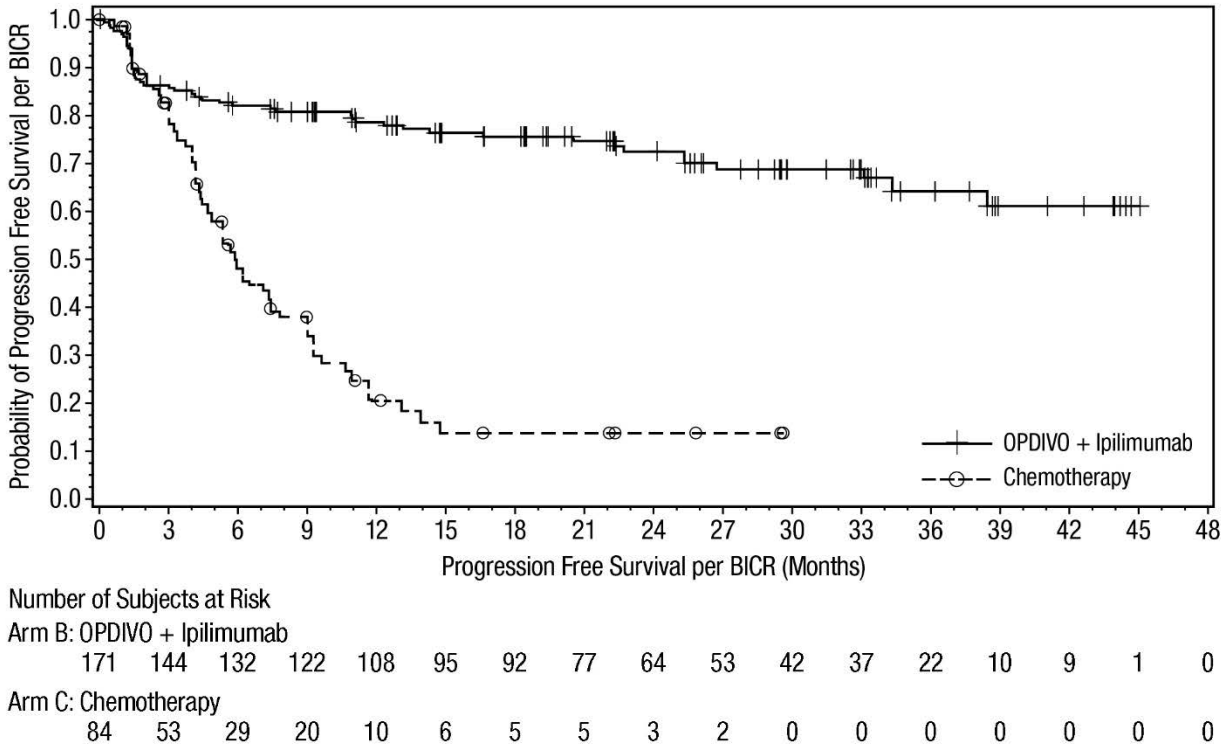
NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 6.1 months at data cutoff date 12Oct2023.

[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0209.

[b] Based on Kaplan-Meier estimates.

[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) per IRT.

Figure 23: Progression-free Survival (First Line OPDIVO + Ipilimumab vs Chemotherapy) - CHECKMATE-8HW



All Lines OPDIVO in combination with ipilimumab

Among 707 patients across all treatment lines who were randomly assigned to OPDIVO in combination with ipilimumab (354) and to OPDIVO (353) single agent, 296 and 286 patients had centrally confirmed MSI-H/dMMR status in the OPDIVO in combination with ipilimumab arm and in the OPDIVO arm, respectively. Patients receiving at least 1 dose of study treatment included 352 of 354 patients randomized to OPDIVO in combination with ipilimumab, and 351 of 353 patients randomized to single agent OPDIVO.

The BICR-assessed PFS and ORR efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the OPDIVO in combination with ipilimumab compared with nivolumab single agent across all treatment lines setting are presented in Table 77 and Figure 24. The comparative results of OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 77: Efficacy Results, All Lines - CHECKMATE-8HW

	OPDIVO and Ipilimumab (n=296)	**OPDIVO (n=286)**
Progression-free Survival		
Disease progression or death n (%)	101 (34)	136 (48)

Table 77: Efficacy Results, All Lines - CHECKMATE-8HW

	OPDIVO and Ipilimumab (n=296)	OPDIVO (n=286)
Median (months)[b] (95% CI)	NR (53.8, NE)	39.3 (22.1, NE)
Hazard ratio[c] (95% CI)	0.62 (0.48, 0.81)	
p-value[a]	0.0003	
Objective Response Rate (ORR)		
Response Rate, n (%) (95% CI)	209 (71%) (65, 76)	165 (58%) (52, 63)
Complete Response Rate, n (%)	90 (30%)	80 (28%)
Partial Response Rate, n (%)	119 (40%)	85 (30%)
p-value[d]	0.0011	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 16.7 months at data cutoff date 28Aug2024.

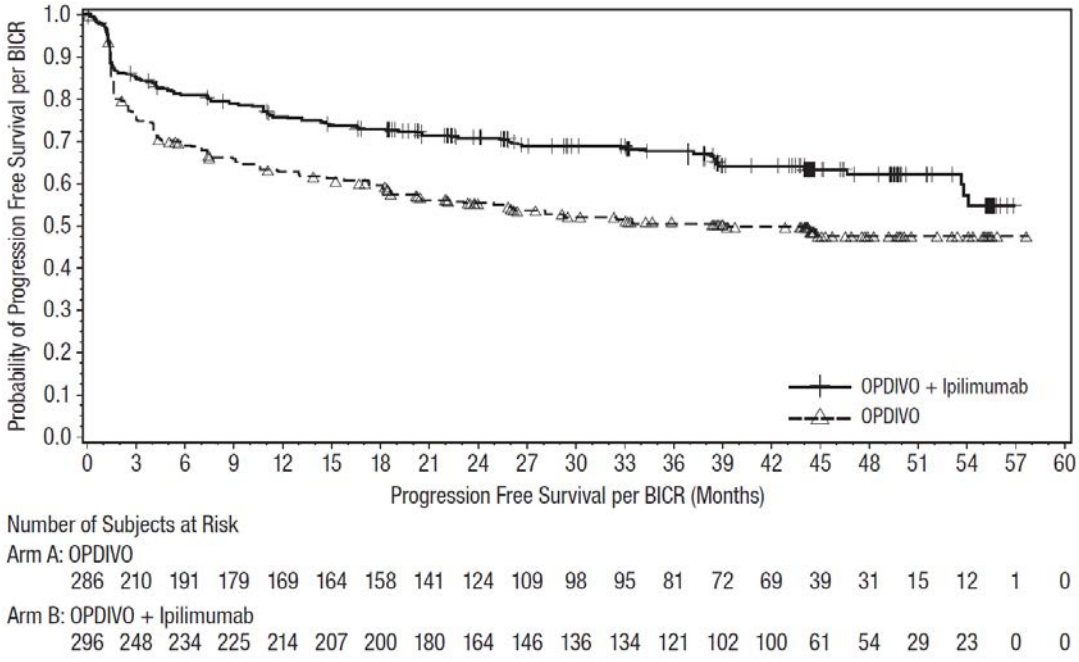
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0095.

[b] Based on Kaplan-Meier estimates.

[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥2) per IRT.

[d] Based on Cochran-Mantel-Haenszel test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.006.

Figure 24: Progression-free Survival (All lines OPDIVO + Ipilimumab vs OPDIVO) - CHECKMATE-8HW



Treatment of MSI-H or dMMR mCRC after Progression Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine- , oxaliplatin- , or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG performance status 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients enrolled in the single agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included ORR and DOR as assessed by BICR using RECIST v1.1.

A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were White. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 7%, 30%, 28%, 19%, and 16% received 0, 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

A total of 119 patients were enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort. The median age was 58 years (range: 21 to 88), with 32% ≥65 years of age and 9% ≥75 years of age; 59% were male and 92% were White. Baseline ECOG performance status was 0 (45%) and 1 (55%), and 29% were reported to have Lynch Syndrome. Across the 119 patients, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 10%, 40%, 24%, and 15% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results for each of these single-arm cohorts are shown in Table 78.

Table 78: Efficacy Results - CHECKMATE-142

	OPDIVO[a] MSI-H/dMMR Cohort		OPDIVO and Ipilimumab[b] MSI-H/dMMR Cohort	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
Overall Response Rate per BICR; n (%)	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI)[c]	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
Duration of Response				
Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

[a] Minimum follow-up 33.7 months for all patients treated with OPDIVO (n=74).

[b] Minimum follow-up 27.5 months for all patients treated with OPDIVO and ipilimumab (n=119).

[c] Estimated using the Clopper-Pearson method.

14.12 Hepatocellular Carcinoma

Treatment of Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

CHECKMATE-9DW (NCT04039607) was a randomized (1:1), open-label trial in adults (18 years of age or older) with unresectable or metastatic HCC. Patients had histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrollment. The trial excluded patients with active autoimmune disease, brain or leptomeningeal metastases, a history of hepatic encephalopathy (within 12 months of randomization), a platelet count <60,000, clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV).

Patients were randomized to receive either:

- OPDIVO 1 mg/kg administered intravenously over 30 minutes in combination with ipilimumab 3 mg/kg administered intravenously over 30 minutes every 3 weeks, for a

maximum of 4 doses, followed by single agent OPDIVO at 480 mg administered intravenously over 30 minutes every 4 weeks, or

- Investigator's choice:
  - Lenvatinib 8 mg orally daily (if body weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg), or
  - Sorafenib 400 mg orally twice daily

Randomization was stratified by etiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥400 or <400 ng/mL). Study treatment for OPDIVO in combination with ipilimumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Treatment beyond RECIST 1.1 defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy. The primary efficacy outcome measure was OS in all randomized patients. Additional efficacy measures included BICR-assessed ORR and DOR based on RECIST 1.1 criteria.

A total of 668 patients were randomized to receive OPDIVO in combination with ipilimumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. The trial population characteristics were median age 66 years (range: 20 to 89), with 53% ≥65 years old; 82% male; 53% White, 44% Asian, 2.2% Black; 12% Hispanic or Latino, 48% Not Hispanic or Latino, 40% not reported. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection.

Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and 7 were 77%, 20%, and 3%, respectively; 1 patient with Child Pugh 8 was enrolled. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥400 µg/L.

CHECKMATE-9DW demonstrated a statistically significant improvement in OS and ORR. The minimum follow-up was 26.8 months. Efficacy results are shown in Table 79 and Figure 25.

Table 79: Efficacy Results - CHECKMATE-9DW

	OPDIVO and Ipilimumab (n=335)	**Lenvatinib or Sorafenib (n=333)**
Overall Survival		
Deaths (%)	194 (58%)	228 (68%)
Median (months)	23.7	20.6

Table 79: Efficacy Results - CHECKMATE-9DW

	OPDIVO and Ipilimumab (n=335)	**Lenvatinib or Sorafenib (n=333)**
(95% CI)	(18.8, 29.4)	(17.5, 22.5)
Hazard ratio (95% CI)[a]	0.79 (0.65, 0.96)	
p-value[b]	0.0180	
Overall Response Rate, n (%)[c]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[d]	<0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[c]		
Median (95% CI)	30.4 (21.2, NR[e])	12.9 (10.2, 31.2)
Range	1.5+, 36.9+	2.1+, 32.5+

[a] Based on stratified Cox proportional hazard model.

[b] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257.

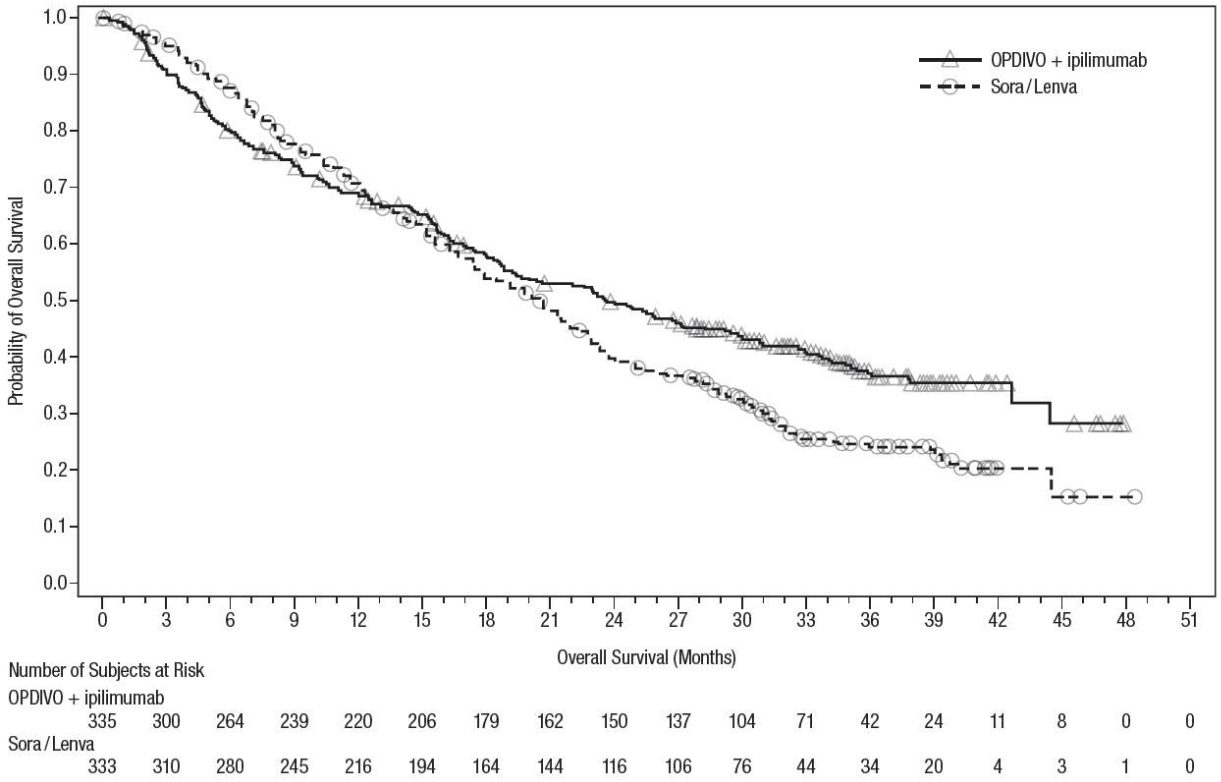
[c] Assessed by BICR using RECIST 1.1.

[d] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤0.025.

[e] NR: Not Reached.

+ Censored observation.

Figure 25: Overall Survival - CHECKMATE-9DW



Previously Treated Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and then every 12 weeks thereafter. The major efficacy outcome measure was confirmed overall response rate as assessed by BICR using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

The efficacy of OPDIVO in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16%

and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 80. The results for OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table 80: Efficacy Results - Cohort 4 of CHECKMATE-040

	OPDIVO and Ipilimumab (Cohort 4) (n=49)
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)
(95% CI)[b]	(20, 48)
Complete response	4 (8%)
Partial response	12 (24%)
Duration of Response per BICR,[a] RECIST v1.1	n=16
Range (months)	4.6, 30.5+
Percent with duration ≥6 months	88%
Percent with duration ≥12 months	56%
Percent with duration ≥24 months	31%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)
(95% CI)[b]	(22, 50)
Complete response	6 (12%)
Partial response	11 (22%)

[a] Confirmed by BICR.

[b] Confidence interval is based on the Clopper and Pearson method.

14.13 Esophageal Cancer

Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

CHECKMATE-577 (NCT02743494) was a randomized, multicenter, double-blind trial in 794 patients with completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following concurrent chemoradiotherapy (CRT). Patients were randomized (2:1) to receive either OPDIVO 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Treatment was until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. Enrollment required complete resection within 4 to 16 weeks prior to randomization. The trial excluded patients who did not receive CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any

condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Randomization was stratified by tumor PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). The major efficacy outcome measure was disease-free survival (DFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant from the primary resected site) or death, from any cause, whichever occurred first as assessed by the investigator prior to subsequent anti-cancer therapy. Patients on treatment underwent imaging for tumor recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

The trial population characteristics were: median age 62 years (range: 26 to 86), 36% were ≥65 years of age, 85% were male, 15% were Asian, 82% were White, and 1.1% were Black. Disease characteristics were AJCC Stage II (35%) or Stage III (65%) at initial diagnosis carcinoma, EC (60%) or GEJC (40%) at initial diagnosis, with pathologic positive lymph node status (58%) at study entry and histological confirmation of predominant adenocarcinoma (71%) or squamous cell carcinoma (29%). The baseline Tumor PD-L1 status ≥1% was positive for 16% of patients and negative for 72% of patients. Baseline ECOG performance status was 0 (58%) or 1 (42%).

CHECKMATE-577 demonstrated a statistically significant improvement in DFS for patients randomized to the OPDIVO arm as compared with the placebo arm. DFS benefit was observed regardless of tumor PD-L1 expression and histology.

Efficacy results are shown in Table 81 and Figure 26.

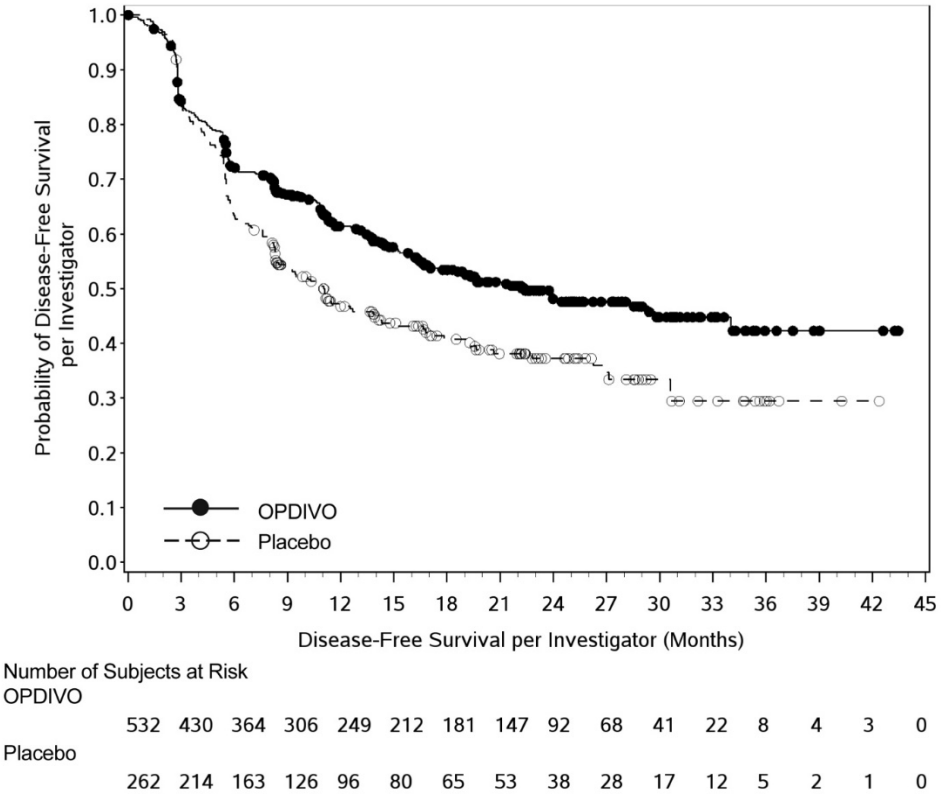
Table 81: Efficacy Results - CHECKMATE-577

	OPDIVO (n=532)	**Placebo (n=262)**
Disease-free Survival		
Number of events, n (%)	241 (45%)	155 (59%)
Median (months) (95% CI)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)
Hazard ratio[a] (95% CI)	0.69 (0.56, 0.85)	
p-value[b]	0.0003	

[a] Based on a stratified proportional hazards model.

[b] Based on a stratified log-rank test.

Figure 26: Disease-free Survival - CHECKMATE-577



First-line Treatment of Unresectable Advanced or Metastatic ESCC Whose Tumors Express PD-L1 (≥1)

CHECKMATE-648 (NCT03143153) was a randomized, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC (squamous or adenosquamous histology). The trial enrolled patients whose tumor was evaluable for tumor cell (TC) PD-L1 expression [also called PD-L1 tumor proportion score (TPS)], which was evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. A retrospective scoring of a patient's tumor PD-L1 status using Combined Positive Score (CPS), was also conducted using the PD-L1-stained tumor specimens used for randomization. Patients were not amenable to chemoradiation or surgery with curative intent. Prior treatment with curative intent was allowed if completed more than six months prior to trial enrollment. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. Patients were randomized to receive one of the following treatments:

- OPDIVO 240 mg on days 1 and 15, fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.

- Fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).

Patients received OPDIVO until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent.

Randomization was stratified by TC PD-L1 expression (≥1% vs. <1% or indeterminate), region (East Asia vs. Rest of Asia vs. Rest of World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2). The major efficacy outcome measures were OS and BICR-assessed PFS in patients with TC PD-L1 expression ≥ 1%. Additional efficacy measures included OS in all randomized patients, BICR-assessed PFS in all randomized patients, and ORR assessed by BICR in TC PD-L1 expression ≥ 1% and in all randomized patients. The tumor assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 970 patients were randomized in the CHECKMATE-648 study, among whom 965 and 906 patients had quantifiable TC PD-L1 expression and CPS at baseline, respectively; 85% (824/970) had tumors with PD-L1 CPS ≥1. The trial population characteristics in patients with PD-L1 CPS ≥1 were: median age 63 years (range: 26 to 90), 46% were ≥65 years of age, 82% were male, 71% were Asian, 25% were White, and 1.2% were Black or African American. Patients had histological confirmation of squamous cell carcinoma (99%) or adenosquamous cell carcinoma (1.7%) in the esophagus. Baseline ECOG performance status was 0 (44.0%) or 1 (54%).

A statistically significant improvement in OS was demonstrated in patients randomized to OPDIVO in combination with chemotherapy and patients randomized to OPDIVO in combination with ipilimumab compared with chemotherapy. An exploratory analysis of OS in patients with PD-L1 CPS <1 showed a HR of 0.98 (95% CI 0.50, 1.95) for the comparison of OPDIVO in combination with chemotherapy, and the exploratory analysis OS in patients with PD-L1 CPS <1 showed a HR of 1.0 (95% CI 0.52, 1.94) for the comparison of OPDIVO in combination with ipilimumab; these results indicate that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1. Efficacy results are shown in Table 82 and Figures 27 and 28.

Table 82: Efficacy Results - CHECKMATE-648

	OPDIVO with Cisplatin and Fluorouracil (n=158)	**OPDIVO and Ipilimumab (n=158)**	**Cisplatin and Fluorouracil (n=157)**	**OPDIVO with Cisplatin and Fluorouracil (n=278)**	**OPDIVO and Ipilimumab (n=266)**	**Cisplatin and Fluorouracil (n=280)**
	TC PD-L1 expression ≥1%			**PD-L1 CPS ≥1**		
Overall Survival						
Deaths (%)	98 (62)	106 (67)	121 (77)	177 (64)	179 (67)	205 (73)

Table 82: Efficacy Results - CHECKMATE-648

	OPDIVO with Cisplatin and Fluorouracil (n=158)	OPDIVO and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)	OPDIVO with Cisplatin and Fluorouracil (n=278)	OPDIVO and Ipilimumab (n=266)	Cisplatin and Fluorouracil (n=280)
	TC PD-L1 expression ≥1%			PD-L1 CPS ≥1		
Median (months) (95% CI)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)	13.8 (12.0, 16.1)	12.7 (10.9, 15.5)	9.8 (8.8, 11.6)
Hazard ratio (95% CI)[b]	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-	0.69 (0.57, 0.85)	0.76 (0.62, 0.93)	-
p-value[c]	<0.0001[S1]	0.0010[S2]	-	-	-	-
Progression-free Survival[a]						
Disease progression or death (%)	117 (74)	123 (78)	100 (64)	201 (72)	206 (77)	184 (66)
Median (months) (95% CI)	6.9 (5.7, 8.3)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)	5.8 (5.5, 7.0)	2.8 (2.6, 4.2)	5.6 (4.2, 5.9)
Hazard ratio (95% CI)[b]	0.65 (0.49, 0.86)	1.02 (0.78, 1.34)	-	0.8 (0.7, 1.0)	1.2 (1.0, 1.5)	-
p-value[c]	0.0023[S3]	NS	-	-	-	-
Overall Response Rate, n (%)[a, NT]	84 (53.2)	56 (35.4)	31 (19.7)	135 (49)	74 (28)	76 (27)
(95% CI)	(45.1, 61.1)	(28.0, 43.4)	(13.8, 26.8)	(42.5, 54.6)	(22.5, 33.6)	(22.0, 32.8)
Complete response (%)	26 (16.5)	28 (17.7)	8 (5.1)	39 (14)	32 (12.0)	18 (6.4)
Partial response (%)	58 (36.7)	28 (17.7)	23 (14.6)	96 (35)	42 (15.8)	58 (20.7)
Duration of Response (months)[a]						
Median (95% CI)	8.4 (6.9, 12.4)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)	8.2 (6.7, 11.1)	11.8 (7.1, 23.6)	6.9 (5.7, 8.2)
Range	1.4+, 34.6	1.4+, 34.5+	1.4+, 31.8+	1.4+, 35.9+	1.4+, 34.5+	1.4+, 31.8+

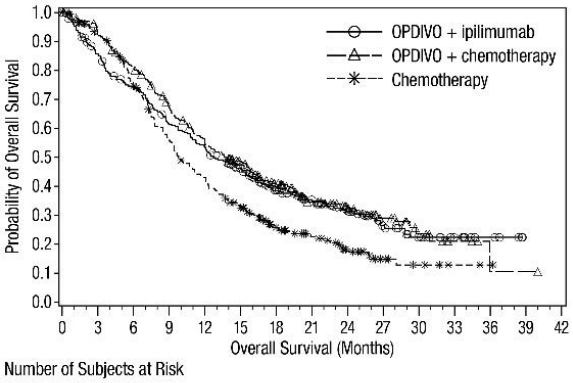
[a] Assessed by BICR.

[b] Based on stratified Cox proportional hazard model. Hazard ratios are reported for each OPDIVO containing arm compared to chemotherapy within each analysis population.

[c] Based on a stratified 2-sided log-rank test.
[S1, S2, S3] Significant p-value compared to stopping boundary of 0.005, 0.014, and 0.015 respectively.
NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure.

Figure 27: Overall Survival – CHECKMATE-648

(A) OS in CPS ≥1



(B) OS in TC PD-L1 ≥1%

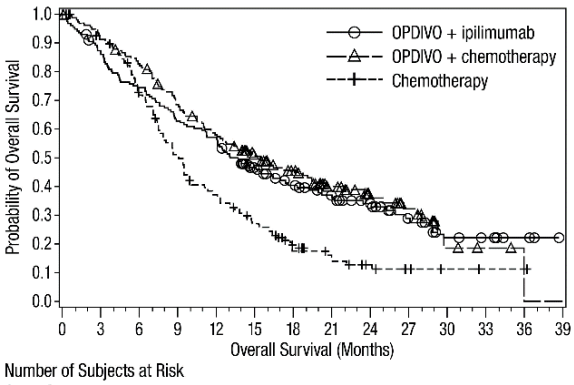
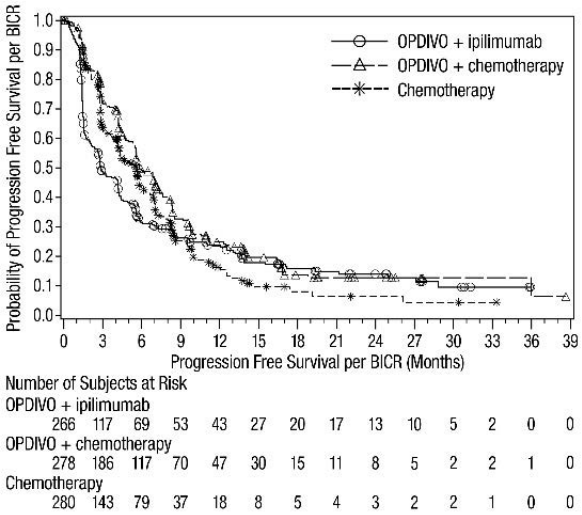
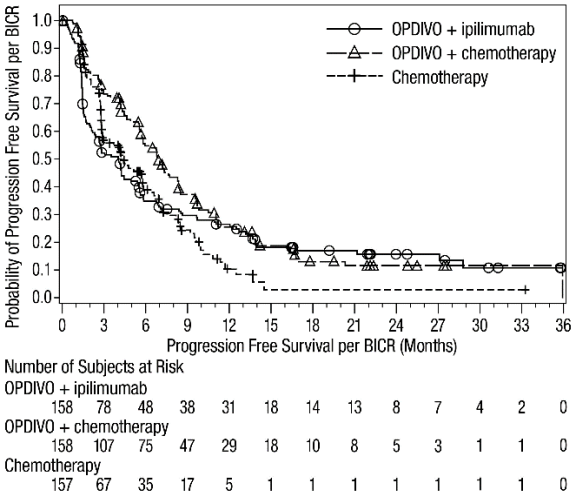


Figure 28: Progression-free Survival – CHECKMATE-648

(A) PFS in CPS ≥1



(B) PFS in TC PD-L1 ≥1%



Previously Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

ATTRACTION-3 (NCT02569242) was a multicenter, randomized (1:1), active-controlled, open-label trial in patients with unresectable advanced, recurrent, or metastatic ESCC, who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen. The trial

enrolled patients regardless of PD-L1 status, but tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, or had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients were randomized to receive OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m^2 intravenously every 3 weeks) or paclitaxel (100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off).

Randomization was stratified by region (Japan vs. Rest of World), number of organs with metastases (≤1 vs. ≥2), and PD-L1 status (≥1% vs. <1% or indeterminate). Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. The tumor assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were ORR and PFS as assessed by the investigator using RECIST v1.1 and DOR.

A total of 419 patients were randomized; 210 to the OPDIVO arm and 209 to the investigator's choice arm (docetaxel: 31%, paclitaxel: 69%). The trial population characteristics were: median age 65 years (range: 33 to 87), 53% were ≥65 years of age, 87% were male, 96% were Asian and 4% were White. Sixty-seven percent of patients had received one prior systemic therapy regimen and 26% had received two prior systemic therapy regimens prior to enrolling in ATTRACTION-3. Baseline ECOG performance status was 0 (50%) or 1 (50%).

ATTRACTION-3 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice of taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. OS results by PD-L1 CPS level (<1 and ≥1) were not studied. The minimum follow-up was 17.6 months. Efficacy results are shown in Table 83 and Figure 29.

Table 83: Efficacy Results - ATTRACTION-3

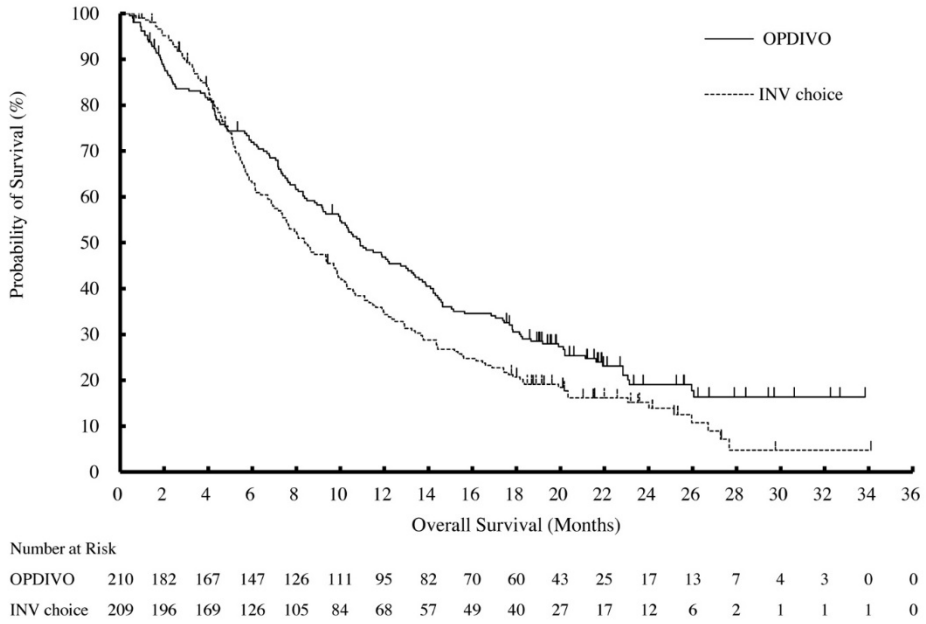
	OPDIVO (n=210)	**Docetaxel or Paclitaxel (n=209)**
Overall Survival[a]		
Deaths (%)	160 (76%)	173 (83%)
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Overall Response Rate[d]	33 (19.3)	34 (21.5)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response (%)	1 (0.6)	2 (1.3)

Table 83: Efficacy Results - ATTRACTION-3

	OPDIVO (n=210)	Docetaxel or Paclitaxel (n=209)
Partial response (%)	32 (18.7)	32 (20.3)
Median duration of response (months) (95% CI)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
p-value[e]	0.6323	
Progression-free Survival[a, f]		
Disease progression or death (%)	187 (89)	176 (84)
Median (months) (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	

[a] Based on ITT analysis
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] Based on Response Evaluable Set (RES) analysis, n=171 in OPDIVO group and n=158 in investigator's choice group.
[e] Based on stratified Cochran-Mantel-Haenszel test; p-value not significant.
[f] PFS not tested due to pre-specified hierarchical testing strategy.

Figure 29: Overall Survival - ATTRACTION-3



Of the 419 patients, 48% had PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. The remaining 52% had PD-L1 negative ESCC defined as <1% of tumor cells expressing PD-L1.

In a pre-specified exploratory analysis by PD-L1 status, the hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the OPDIVO and investigator's choice arms, respectively, in the PD-L1 positive subgroup. In the PD-L1 negative subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the OPDIVO and investigator's choice arms, respectively.

14.14 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma Whose Tumors Express PD-L1 (≥1)

CHECKMATE-649 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory (tumor cell [TC] and Combined Positive Score [CPS]). The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy (n=789) or chemotherapy (n=792). Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom chemotherapy was discontinued, OPDIVO monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation.

Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (mFOLFOX6 vs. CapeOX). The major efficacy outcome measures, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Additional efficacy outcome measures included OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and ORR and DOR as assessed by BICR in patients with PD-L1 CPS ≥1 and ≥5, and in all randomized patients. Tumor assessments were conducted per RECIST v1.1 every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 1581 patients were randomized in the CHECKMATE-649 study, among whom 1296 and 955 had baseline PD-L1 CPS ≥1 and CPS ≥5 respectively. The trial population characteristics in patients with PD-L1 CPS ≥ 1 were: median age 62 years (range: 18 to 90), 40% were ≥65 years of age, 72% were male, 23% were Asian, and 69% were White, and 1% were Black or African American. Baseline ECOG performance status was 0 (42%) or 1 (58%). Seventy percent of patients had adenocarcinoma tumors in the stomach, 17% in the gastroesophageal junction, and 13% in the esophagus.

CHECKMATE-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated

for all randomized patients and patients with PD-L1 CPS ≥1. Exploratory analysis of OS in the CPS <1 population showed a hazard ratio of 0.85 (95% CI: 0.63, 1.15), indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 84 and Figures 30, and 31.

Table 84: Efficacy Results - CHECKMATE-649

	OPDIVO and mFOLFOX6 or CapeOX (n=641)	**mFOLFOX6 or CapeOX (n=655)**	**OPDIVO and mFOLFOX6 or CapeOX (n=473)**	**mFOLFOX6 or CapeOX (n=482)**
	PD-L1 CPS ≥1		**PD-L1 CPS ≥5**	
Overall Survival				
Deaths (%)	434 (68)	492 (75)	309 (65)	362 (75)
Median (months) (95% CI)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (95% CI)[a]	0.77 (0.68, 0.88)		0.71 (0.61, 0.83)	
p-value[b]	<0.0001		<0.0001	
Progression-free Survival[c]				
Disease progression or death (%)	454 (70.8)	472 (72.1)	328 (69.3)	350 (72.6)
Median (months) (95% CI)	7.5 (7.0, 8.4)	6.9 (6.1, 7.0)	7.7 (7.0, 9.2)	6.0 (5.6, 6.9)
Hazard ratio (95% CI)[a]	0.74 (0.65, 0.85)		0.68 (0.58, 0.79)	
p-value[b]	[e]		<0.0001	
Overall Response Rate, n (%)[c,d]	314 (49)	249 (38)	237 (50)	184 (38)
(95% CI)	(45, 53)	(34, 42)	(46, 55)	(34, 43)
Complete response (%)	65 (10)	42 (6)	55 (12)	34 (7)
Partial response (%)	249 (39)	207 (32)	182 (38)	150 (31)
Duration of Response (months)[c,d]				
Median (95% CI) Range	8.5 (7.7, 10.3) 1.1+, 29.6+	6.9 (5.8, 7.6) 1.2+, 30.8+	9.5 (8.1, 11.9) 1.1+, 29.6+	6.9 (5.6, 7.9) 1.2+, 30.8+

[a] Based on stratified Cox proportional hazard model.

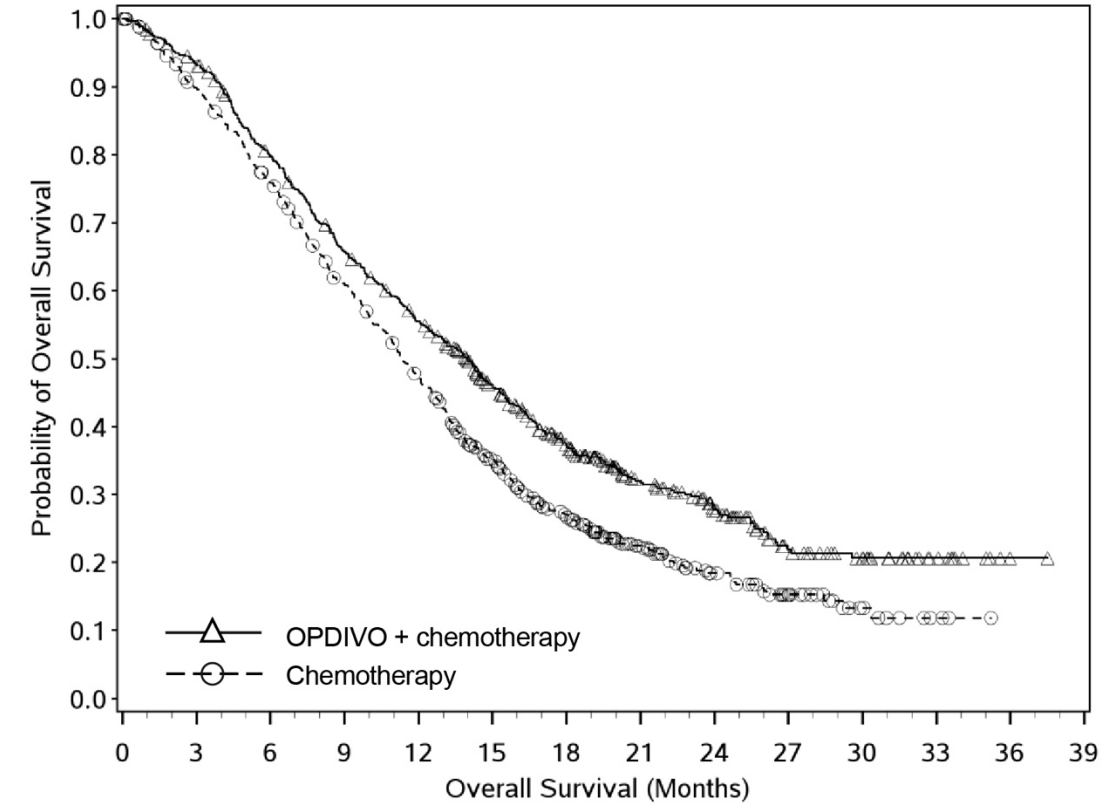
[b] Based on stratified log-rank test.

[c] Assessed by BICR.

[d] Based on confirmed response.

[e] Not evaluated for statistical significance.

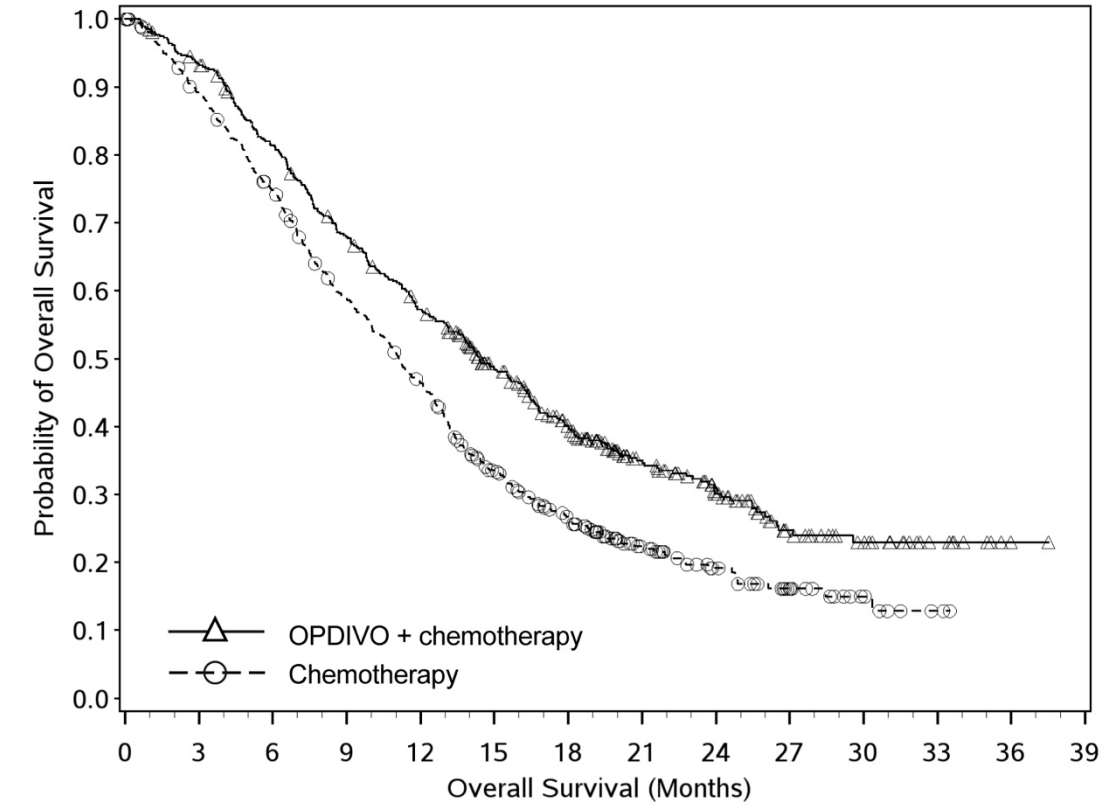
Figure 30: Overall Survival (PD-L1 CPS ≥1) - CHECKMATE-649



Number of Subjects at Risk

OPDIVO + chemotherapy	641	595	502	412	344	254	183	118	80	40	28	11	1	0
Chemotherapy	655	575	483	383	292	194	131	77	45	25	10	3	0	0

Figure 31: Overall Survival (PD-L1 CPS ≥5) - CHECKMATE-649



An exploratory analysis of OS in the 44 patients with MSI-H tumors showed a HR of 0.37 (95% CI: 0.16, 0.87).

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) Injection is a clear to opalescent, colorless to pale-yellow solution in a single-dose vial available as follows:

Carton Contents	NDC
40 mg/4 mL (10 mg/mL) single-dose vial	0003-3772-11
100 mg/10 mL (10 mg/mL) single-dose vial	0003-3774-12
120 mg/12 mL (10 mg/mL) single-dose vial	0003-3756-14
240 mg/24 mL (10 mg/mL) single-dose vial	0003-3734-13

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original package until time of use. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.1)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

Reference ID: 5595654

MEDICATION GUIDE
OPDIVO® (op-DEE-voh)
(nivolumab)
injection

Read this Medication Guide before you start receiving OPDIVO and before each infusion. There may be new information. If your healthcare provider prescribes OPDIVO in combination with ipilimumab, also read the Medication Guide that comes with ipilimumab. If your healthcare provider prescribes OPDIVO in combination with cabozantinib, also read the Patient Information that comes with cabozantinib. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OPDIVO?

OPDIVO is a medicine that may treat certain cancers by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. You may have more than one of these problems at the same time. Some of these problems may happen more often when OPDIVO is used in combination with another therapy.

Call or see your healthcare provider right away if you develop any new or worsening signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- swollen lymph nodes
- painful sore or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with OPDIVO. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Rejection of a transplanted organ or tissue. Your healthcare provider should tell you what signs and symptoms you should report and monitor you depending on the type of organ transplant that you have had.

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO, if you have severe side effects.

What is OPDIVO?

OPDIVO is a prescription medicine used to treat:

- **adults and children 12 years of age and older with a type of skin cancer called melanoma.**
  - OPDIVO may be used alone or in combination with ipilimumab to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma), **or**
  - OPDIVO may be used alone to help prevent Stage IIB, Stage IIC, Stage III or Stage IV melanoma from coming back after it has been completely removed by surgery.
- **adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - OPDIVO may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine before you have surgery for early-stage NSCLC,
  - OPDIVO may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine before you have surgery for early-stage NSCLC:
    - that does not have an abnormal EGFR or ALK gene, **and**
    - then may be continued alone after surgery to help prevent your lung cancer from coming back.
  - OPDIVO may be used in combination with ipilimumab as your first treatment for NSCLC:
    - when your lung cancer has spread to other parts of your body (metastatic), **and**
    - your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used in combination with ipilimumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine, as the first treatment of your NSCLC when your lung cancer:
    - has spread, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used when your lung cancer:
    - has spread, **and**
    - you have received chemotherapy that contains platinum, and it did not work or is no longer working, **and**
    - if your tumor has an abnormal EGFR or ALK gene, you should have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
- **adults with a type of cancer that affects the lining of the lungs and chest wall called malignant pleural mesothelioma.**
  - OPDIVO may be used in combination with ipilimumab as your first treatment for malignant pleural mesothelioma that cannot be removed by surgery.
- **adults with a type of kidney cancer called renal cell carcinoma (RCC).**
  - OPDIVO may be used in combination with ipilimumab as your first treatment for certain people when your cancer has spread (advanced RCC).
  - OPDIVO may be used in combination with cabozantinib as your first treatment when your cancer has spread (advanced RCC).
  - OPDIVO may be used alone when your cancer has spread after treatment with other cancer medicines.
- **adults with a type of blood cancer called classical Hodgkin lymphoma (cHL).**
  - OPDIVO may be used if:
    - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
    - you used the medicine brentuximab vedotin before or after your stem cell transplant, **or** you received at least 3 kinds of treatment including a stem cell transplant that uses your own stem cells (autologous).
- **adults with head and neck cancer (squamous cell carcinoma).**
  - OPDIVO may be used when your head and neck cancer:
    - has come back or spread, **and**
    - you have received chemotherapy that contains platinum and it did not work or is no longer working.
- **adults with a type of cancer of the lining of the urinary tract called urothelial carcinoma (UC).**
  - OPDIVO may be used to help prevent cancer of the urinary tract from coming back after it was removed by surgery.
  - OPDIVO may be used in combination with chemotherapy medicines cisplatin and gemcitabine as your first treatment when your urinary tract cancer has spread or cannot be removed by surgery.

- OPDIVO may be used when your urinary tract cancer has spread (locally advanced or metastatic), **and**:
  - you have received chemotherapy that contains platinum, and it did not work or is no longer working, **or**
  - your cancer worsened within 12 months of treatment with chemotherapy that contains platinum, either before or after surgery to remove your cancer.

- **adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).**
  - OPDIVO may be used in combination with ipilimumab when your colon or rectal cancer:
    - cannot be removed with surgery, or has spread, **and**
    - is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
  - OPDIVO may be used alone when your colon or rectal cancer:
    - has spread, **and**
    - is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
    - you have received treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.

- **adults with a type of liver cancer called hepatocellular carcinoma (HCC).**
  - OPDIVO may be used in combination with ipilimumab as your first treatment when your liver cancer:
    - cannot be removed by surgery, **or**
    - has spread.
  - OPDIVO may be used in combination with ipilimumab when your liver cancer:
    - cannot be removed by surgery, **or**
    - has spread, and
    - you have received prior treatment with sorafenib.

- **adults with cancer of the tube that connects your throat to your stomach (esophageal cancer).**
  - OPDIVO may be used to help prevent your esophageal or gastroesophageal junction cancer from coming back when:
    - your esophageal or gastroesophageal junction cancer has been treated with chemoradiation followed by surgery to completely remove the cancer, **but**
    - some cancer cells were still present in the removed tumor or lymph nodes.
  - OPDIVO may be used in combination with chemotherapy that contains fluoropyrimidine and platinum as your first treatment when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery, or has spread, **and**
    - your tumors are positive for PD-L1.
  - OPDIVO may be used in combination with ipilimumab as your first treatment when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery, or has spread, **and**
    - your tumors are positive for PD-L1.
  - OPDIVO may be used alone when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery, and has come back or spread, **and**
    - you have received chemotherapy that contains fluoropyrimidine and platinum.

- **adults with cancer of the stomach (gastric cancer), cancer where the esophagus joins the stomach (gastroesophageal junction cancer), and in adults with esophageal adenocarcinoma.**
  - OPDIVO may be used in combination with chemotherapy that contains fluoropyrimidine and platinum when your gastric, gastroesophageal junction, or esophageal cancer:
    - cannot be removed with surgery, or has spread, **and**
    - your tumors are positive for PD-L1.

It is not known if OPDIVO is safe and effective in children younger than 12 years of age with melanoma or MSI-H or dMMR metastatic colorectal cancer.

It is not known if OPDIVO is safe and effective in children for the treatment of any other cancers.

Before receiving OPDIVO, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus.
- have received an organ transplant, including corneal transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area in the past and have received other medicines that are like OPDIVO
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.

  Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start receiving OPDIVO.
- You should use an effective method of birth control during treatment and for 5 months after your last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.

- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. Do not breastfeed during treatment and for 5 months after your last dose of OPDIVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive OPDIVO?

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 30 minutes.
- When OPDIVO is used alone, it is usually given every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with ipilimumab (except for treating NSCLC), OPDIVO is usually given every 3 weeks, for up to 4 doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- For NSCLC before you have surgery, OPDIVO is given in combination with platinum-containing chemotherapy and another chemotherapy medicine every 3 weeks for 3 cycles. In some cases, OPDIVO is used in combination with chemotherapy every 3 weeks for up to 4 cycles before you have surgery, followed by OPDIVO used alone every 4 weeks after you have surgery for up to 1 year.
- For NSCLC that has spread to other parts of your body, when OPDIVO is used in combination with ipilimumab, OPDIVO is given every 3 weeks, and ipilimumab is given every 6 weeks for up to 2 years. Your healthcare provider will determine if you will also need to receive chemotherapy every 3 weeks for 2 cycles.
- For malignant pleural mesothelioma, OPDIVO is given every 3 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- For RCC, when used in combination with cabozantinib, OPDIVO is usually given every 2 weeks or 4 weeks depending on the dose you are receiving. Cabozantinib is given once daily by mouth.
- For UC that has spread to other parts of your body or cannot be removed by surgery, when OPDIVO is used in combination with chemotherapy medicines cisplatin and gemcitabine, OPDIVO is given every 3 weeks for up to 6 cycles. Chemotherapy will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with fluoropyrimidine- and platinum-containing chemotherapy for treating esophageal squamous cell carcinoma (ESCC), OPDIVO is given either every 2 weeks or every 4 weeks, for up to 2 years.
- When OPDIVO is used in combination with ipilimumab for esophageal squamous cell carcinoma, OPDIVO is given every 2 weeks or 3 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- For gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, when used in combination with fluoropyrimidine and platinum-containing chemotherapy, OPDIVO is given every 2 weeks or 3 weeks depending on the dose you are receiving, for up to 2 years. Chemotherapy will be given on the same day.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects, including:

- **See "What is the most important information I should know about OPDIVO?"**
- **Severe infusion reactions.** Tell your healthcare provider or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - shortness of breath or wheezing
  - dizziness
  - feel like passing out
  - fever
  - back or neck pain
- **Complications of stem cell transplant that uses donor stem cells (allogeneic).** These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with OPDIVO. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

The most common side effects of OPDIVO when used alone include:

- feeling tired
- rash
- pain in muscles, bones, and joints
- constipation
- decreased appetite
- back pain

- itching
- diarrhea
- nausea
- weakness
- cough
- shortness of breath
- upper respiratory tract infection
- fever
- headache
- stomach-area (abdominal) pain
- vomiting
- urinary tract infection

The most common side effects of OPDIVO when used in combination with ipilimumab include:

- feeling tired
- diarrhea
- rash
- itching
- nausea
- pain in muscles, bones, and joints
- fever
- cough
- decreased appetite
- vomiting
- stomach-area (abdominal) pain
- shortness of breath
- upper respiratory tract infection
- headache
- low thyroid hormone levels (hypothyroidism)
- constipation
- decreased weight
- dizziness

The most common side effects of OPDIVO when used in combination with a platinum-containing chemotherapy and another chemotherapy medicine include:

- nausea
- feeling tired
- pain in muscles, bones and joints
- constipation
- decreased appetite
- rash
- vomiting
- numbness, pain, tingling, or burning in your hands and feet

The most common side effects of OPDIVO when used in combination with ipilimumab, a platinum-containing chemotherapy, and another chemotherapy medicine include:

- feeling tired
- pain in muscles, bones, and joints
- nausea
- diarrhea
- rash
- decreased appetite
- constipation
- itching

The most common side effects of OPDIVO when used in combination with cabozantinib include:

- diarrhea
- feeling tired or weak
- liver problems. See "**What is the most important information I should know about OPDIVO**?"
- rash, redness, pain, swelling or blisters on the palms of your hands or soles of your feet
- mouth sores
- rash
- high blood pressure
- low thyroid hormone levels
- pain in muscles, bones, and joints
- decreased appetite
- nausea
- change in the sense of taste
- stomach-area (abdominal) pain
- cough
- upper respiratory tract infection

The most common side effects of OPDIVO when used in combination with fluoropyrimidine and platinum-containing chemotherapy include:

- nausea
- numbness, pain, tingling, or burning in your hands or feet
- decreased appetite
- feeling tired
- constipation
- mouth sores
- diarrhea
- vomiting
- stomach-area (abdominal) pain
- pain in muscles, bones, and joints

These are not all the possible side effects of OPDIVO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OPDIVO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about OPDIVO that is written for health professionals.

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA U.S. License No. 1713

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For more information, call 1-855-673-4861 or go to www.OPDIVO.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2025

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
One vial of 4 mL contains 40 mg of nivolumab.
One vial of 10 mL contains 100 mg of nivolumab.
One vial of 12 mL contains 120 mg of nivolumab.
One vial of 24 mL contains 240 mg of nivolumab.

Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect

Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1).

Non-small cell lung cancer (NSCLC)

OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Neoadjuvant treatment of NSCLC

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria).

Neoadjuvant and adjuvant treatment of NSCLC

OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria).

Malignant pleural mesothelioma (MPM)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Renal cell carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see section 5.1).

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1).

Classical Hodgkin lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

Squamous cell cancer of the head and neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1).

Urothelial carcinoma

OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Adjuvant treatment of urothelial carcinoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:

- first-line treatment of unresectable or metastatic colorectal cancer;
- treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (see section 5.1).

Oesophageal squamous cell carcinoma (OSCC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (see section 5.1).

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

Hepatocellular carcinoma (HCC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

PD-L1 testing

If specified in the indication, patient selection for treatment with OPDIVO based on the tumour expression of PD-L1 should be assessed by a CE-marked in vitro IVD medical device test. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

MSI/MMR testing

If specified in the indication, patient selection for treatment with OPDIVO based on MSI-H/dMMR tumour status should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

Posology

OPDIVO as monotherapy
The recommended dose of OPDIVO is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks depending on the indication and population (see sections 5.1 and 5.2), as presented in Table 1.

Table 1: Recommended dose and infusion time for intravenous administration of nivolumab monotherapy

Indication*	**Recommended dose and infusion time**
Melanoma (advanced or adjuvant treatment)	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes or over 30 minutes (adjuvant melanoma, see section 5.1)
	Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes
Renal cell carcinoma Muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Oesophageal or gastro-oesophageal junction cancer (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks, followed by 480 mg every 4 weeks over 30 minutes
Non-small cell lung cancer Classical Hodgkin lymphoma Squamous cell cancer of the head and neck Urothelial carcinoma Oesophageal squamous cell carcinoma	240 mg every 2 weeks over 30 minutes

*As per monotherapy indication in section 4.1.

If melanoma, RCC, OC, GEJC or MIUC (adjuvant treatment) patients need to be switched from the 240 mg every 2 weeks schedule to the 480 mg every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 240 mg every 2 weeks schedule, the first 240 mg dose should be administered four weeks after the last 480 mg dose.

OPDIVO in combination with ipilimumab

Melanoma
In adults and adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks (see sections 5.1 and 5.2), as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; **or**
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks.

In adolescents 12 years of age and older and weighing less than 50 kg, the recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every

3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 3 mg/kg every 2 weeks **or** 6 mg/kg every 4 weeks (see sections 5.1 and 5.2), as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 3 mg/kg every 2 weeks; **or**
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 6 mg/kg every 4 weeks.

Table 2: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for melanoma

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	Adults and adolescents 12 years of age and older: 1 mg/kg over 30 minutes	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes
Ipilimumab	Adults and adolescents 12 years of age and older: 3 mg/kg over 30 minutes	-

Malignant pleural mesothelioma

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is continued for up to 24 months in patients without disease progression.

Renal cell carcinoma

The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 3. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks.

Table 3: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for RCC

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Ipilimumab	1 mg/kg over 30 minutes	-

dMMR or MSI-H colorectal cancer

The recommended dose for first-line treatment of dMMR or MSI-H CRC is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, as presented in Table 4. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab

and ipilimumab. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose in patients who received prior fluoropyrimidine-based combination chemotherapy for dMMR or MSI-H CRC is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab monotherapy administered intravenously 240 mg every 2 weeks, as presented in Table 4. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab.

Table 4: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for dMMR or MSI-H CRC

		Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	First-line	240 mg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
	After prior fluoropyrimidine-based combination chemotherapy	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes
Ipilimumab		1 mg/kg over 30 minutes	-

Oesophageal squamous cell carcinoma
The recommended dose is either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30 minutes in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Hepatocellular carcinoma
The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for up to 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks (see sections 5.1 and 5.2), as presented in Table 5. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks or 480 mg every 4 weeks.

Table 5: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for HCC

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	1 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
Ipilimumab	3 mg/kg over 30 minutes	-

OPDIVO in combination with cabozantinib

Renal cell carcinoma
The recommended dose is nivolumab administered intravenously at either 240 mg every 2 weeks **or** 480 mg every 4 weeks in combination with 40 mg cabozantinib administered orally every day.

Table 6: Recommended doses and infusion times for intravenous administration of nivolumab in combination with oral administration of cabozantinib for RCC

	Combination phase
Nivolumab	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Cabozantinib	40 mg once daily

OPDIVO in combination with ipilimumab and chemotherapy

Non-small cell lung cancer
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered intravenously every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

OPDIVO in combination with chemotherapy

Neoadjuvant treatment of non-small cell lung cancer
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles (see section 5.1).

Neoadjuvant and adjuvant treatment of non-small cell lung cancer
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 4 cycles in the neoadjuvant phase, followed by adjuvant treatment with nivolumab 480 mg as monotherapy every 4 weeks. Treatment is recommended until disease progression or recurrence, unacceptable toxicity, or up to 13 cycles (see section 5.1).

Oesophageal squamous cell carcinoma
The recommended dose of nivolumab is 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks **or** 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

First-line treatment of unresectable or metastatic urothelial carcinoma
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes **or** at 480 mg every 4 weeks over 30 minutes (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

Duration of treatment
Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab or other therapeutic agents, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).

For adjuvant therapy, the maximum treatment duration with OPDIVO is 12 months.

For OPDIVO in combination with cabozantinib, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the Summary of Product Characteristics (SmPC) for cabozantinib.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 7. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. When nivolumab is administered in combination with other therapeutic agents, refer to the SmPC of these other combination therapeutic agents regarding dosing.

Table 7: Recommended treatment modifications for OPDIVO or OPDIVO in combination

Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis - OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	- OPDIVO+ipilimumab[a]	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis without HCC **NOTE:** for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment

Immune-related adverse reaction	Severity	Treatment modification
Immune-related hepatitis with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 and ≤ 10 times ULN or Baseline AST/ALT is > 1 and ≤ 3 times ULN and increases to > 5 and ≤ 10 times ULN or Baseline AST/ALT is > 3 and ≤ 5 times ULN and increases to > 8 and ≤ 10 times ULN.	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	AST/ALT increases to > 10 times ULN or Total bilirubin increases to > 3 times ULN	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[c]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

[a] During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs.

[b] Recommendation for the use of hormone replacement therapy is provided in section 4.4.
[c] The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

OPDIVO as monotherapy or in combination with other therapeutic agents should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also package leaflet).

When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient.

When OPDIVO is administered in combination with chemotherapy, refer to the SmPC of the other combination therapy agents regarding dosing. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.

OPDIVO in combination with cabozantinib in RCC
When OPDIVO is used in combination with cabozantinib, the above treatment modifications in Table 7 also apply to the OPDIVO component. In addition, for liver enzyme elevations, in patients with RCC being treated with OPDIVO in combination with cabozantinib:

- If ALT or AST > 3 times ULN but ≤ 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with cabozantinib, refer to cabozantinib SmPC.
- If ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered.

Special populations

Paediatric population
The safety and efficacy of OPDIVO in children below 18 years of age have not been established except in adolescents 12 years of age and older with melanoma. Currently available data of OPDIVO as monotherapy or in combination with ipilimumab are described in sections 4.2, 4.8, 5.1 and 5.2.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

Renal impairment
Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
Based on the population PK results, no dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2). Data from patients with severe hepatic impairment are too limited to draw conclusions on this population. OPDIVO must be administered with caution in patients with severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see Tables 1, 2, 3, 4 and 5). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm.

OPDIVO must not be administered as an intravenous push or bolus injection.

The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see section 6.6).

When administered in combination with ipilimumab and/or chemotherapy, OPDIVO should be given first followed by ipilimumab (if applicable) and then by chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

For instructions on the preparation and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Assessment of PD-L1 status

When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

Assessment of MSI/MMR status

When assessing the MSI-H and dMMR status of the tumour, it is important that a well-validated and robust methodology is used.

Immune-related adverse reactions

When nivolumab is administered in combination, refer to the SmPC of the other combination therapy agents prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Immune-related adverse reactions have occurred at similar frequencies when OPDIVO was administered in combination with cabozantinib relative to nivolumab monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the OPDIVO component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).
Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Cardiac and pulmonary adverse reactions including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of

electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions (see section 4.2).

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Immune-related pneumonitis
Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related colitis
Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of corticosteroid-refractory immune-related colitis is confirmed addition of an alternative

immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

For Grade 4 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Nivolumab monotherapy should be withheld for Grade 3 diarrhoea or colitis, and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued. Grade 3 diarrhoea or colitis observed with nivolumab in combination with ipilimumab requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related hepatitis
Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related nephritis and renal dysfunction
Severe nephritis and renal dysfunction have been observed with monotherapy treatment or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 or 3 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day

methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related endocrinopathies
Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

For symptomatic hypothyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld and antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, nivolumab or nivolumab in combination with ipilimumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic Grade 2 or 3 hypophysitis, nivolumab or nivolumab in combination with ipilimumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, nivolumab or nivolumab in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions
Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy (see section 4.8). Nivolumab or nivolumab in combination with ipilimumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of SJS and TEN some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab or nivolumab in combination with ipilimumab

should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab or nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended (see section 4.2).

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions
The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis, and myelitis. Cases of Vogt-Koyanagi-Harada syndrome, hypoparathyroidism, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.

The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see section 4.2).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.

Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see section 4.8). In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may

receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Disease-specific precautions

Advanced melanoma
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of nivolumab or nivolumab in combination with ipilimumab (see sections 4.5 and 5.1). Patients with ocular/uveal melanoma were excluded from pivotal clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). Patients with baseline performance score of 2, treated leptomeningeal metastases, ocular/uveal melanoma, autoimmune disease and patients who have had a Grade 3-4 adverse reaction that was related to prior anti-CTLA-4 therapy were included in study CA209172 (see section 5.1). In the absence of data for patients who had been receiving systemic immunosuppressants prior to study entry, and for patients with active brain or leptomeningeal metastases, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1 ≥ 1%). Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see sections 4.8 and 5.1).

Use of nivolumab in melanoma patients with rapidly progressing disease
Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with rapidly progressing disease (see section 5.1).

Adjuvant treatment of melanoma
There are no data on adjuvant treatment in patients with melanoma with the following risk factors (see sections 4.5 and 5.1):

- patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications,
- patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation),
- patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways),
- subjects under the age of 18 years.

In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Non-small cell lung cancer
First-line treatment of NSCLC
Patients with active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, active (untreated) brain metastasis, who received prior systemic treatment for advanced disease, or who had sensitising EGFR mutations or ALK translocations were excluded from the pivotal trial in first-line treatment of NSCLC (see sections 4.5 and 5.1). Limited data are available in elderly patients (≥ 75 years) (see section 5.1). In these patients, nivolumab in combination with ipilimumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Treatment of NSCLC after prior chemotherapy
Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of NSCLC (see sections 4.5 and 5.1). Patients with baseline performance score of 2 were included in study CA209171 (see section 5.1). In the absence of data for patients with autoimmune disease, symptomatic interstitial lung disease, active brain metastases and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see section 5.1).

Neoadjuvant treatment of NSCLC
Patients with a baseline performance score ≥ 2, active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, unresectable or metastatic disease, who received prior anti-cancer treatment for resectable disease, or who had known EGFR mutations or ALK translocations were excluded from the pivotal trial in neoadjuvant treatment of resectable NSCLC (see section 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Neoadjuvant and adjuvant treatment of non-small cell lung cancer
Patients with a baseline performance score ≥ 2, Grade 2 or greater peripheral neuropathy, active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, unresectable or metastatic disease, who received prior anti-cancer treatment for resectable disease, who had EGFR mutations or known ALK translocations, or who had brain metastasis, were excluded from the pivotal trial in neoadjuvant and adjuvant treatment of NSCLC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Malignant pleural mesothelioma
Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the pivotal trial in first-line treatment of MPM (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Renal cell carcinoma
Nivolumab or nivolumab in combination with ipilimumab
Patients with any history of concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab or nivolumab in combination with ipilimumab (see sections 4.5 and 5.1). In the absence of data, nivolumab or nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Nivolumab in combination with cabozantinib
Patients with any active brain metastases, autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab in combination with cabozantinib (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with cabozantinib should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

When nivolumab is given with cabozantinib, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to nivolumab monotherapy in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the SmPC for cabozantinib).

Classical Hodgkin lymphoma
Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Complications of allogeneic haematopoietic stem cell transplant (HSCT) in classical Hodgkin lymphoma
Cases of acute graft-versus-host disease (GVHD) and transplant related mortality (TRM) have been observed from the follow-up of patients with cHL undergoing allogeneic HSCT after previous exposure to nivolumab. Careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case-by-case (see section 4.8).

In patients treated with nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients (see section 4.8).

Head and neck cancer
Patients with a baseline performance score ≥ 2, active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites were excluded from the SCCHN clinical trial (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

Urothelial carcinoma
Treatment of advanced urothelial carcinoma
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Adjuvant treatment of urothelial carcinoma
Patients with a baseline performance score of ≥ 2 (except patients with a baseline performance score of 2 who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy), evidence of disease after surgery, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial of adjuvant treatment of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

dMMR or MSI-H colorectal cancer
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial in dMMR or MSI-H metastatic CRC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Oesophageal squamous cell carcinoma
First-line treatment of OSCC
Patients with a baseline performance score ≥ 2, any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab or chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

In the first-line OSCC trial, a higher number of deaths within 4 months was observed with nivolumab in combination with ipilimumab compared to chemotherapy. Physicians should consider the delayed onset of effect of nivolumab in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease (see section 5.1).

Treatment of OSCC after prior first-line chemotherapy
The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).
Patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with OSCC. A higher number of deaths within 2.5 months after randomisation was observed with nivolumab compared to chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer
Patients with a baseline performance score ≥ 2, who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in oesophageal and gastro-oesophageal junction cancer (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
Patients who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in gastric, GEJ or oesophageal adenocarcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Study CA209649 excluded patients with known HER2-positive status. Patients with undetermined status were allowed in the study and represented 40.3% of patients (see section 5.1).

Hepatocellular carcinoma
Patients who had baseline ECOG performance score ≥ 2, prior liver transplant, Child-Pugh C liver disease, a history of concurrent brain metastases, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in HCC (see sections 4.5 and 5.1). Limited data are available in HCC patients with Child-Pugh B. In the absence of data, nivolumab in combination with ipilimumab followed by nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

In HCC, a higher number of deaths within 6 months was observed with nivolumab in combination with ipilimumab compared to lenvatinib or sorafenib. A higher risk of death may be associated with poor prognostic features. Physicians should consider this risk before initiating treatment with nivolumab in combination with ipilimumab in patients with poor prognostic features.

Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult. Sodium intake could vary in case sodium chloride is used for the dilution steps.

Patient alert card

All prescribers of OPDIVO must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of OPDIVO therapy with the patient. The patient will be provided with the patient alert card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

Other forms of interaction

Systemic immunosuppression
The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of nivolumab in pregnant women. Studies in animals have shown embryofoetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

Breast-feeding

It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies to evaluate the effect of nivolumab on fertility have not been performed. Thus, the effect of nivolumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Nivolumab or nivolumab in combination with ipilimumab may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

4.8 Undesirable effects

Nivolumab as monotherapy (see section 4.2)

Summary of the safety profile
In the pooled dataset of nivolumab as monotherapy across tumour types (n = 4646) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (44%), musculoskeletal pain (28%), diarrhoea (26%), rash (24%),cough (22%), nausea (22%), pruritus (19%), decreased appetite (17%), arthralgia (17%), constipation (16%), dyspnoea (16%), abdominal pain (15%), upper respiratory tract infection (15%), pyrexia (13%), headache (13%), anaemia (13%) and vomiting (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 44%, with 0.3% fatal adverse reactions attributed to study drug. With a minimum of 63 months follow-up in NSCLC, no new safety signals were identified.

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4646) are presented in Table 8. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 8: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia[a], bronchitis
Rare	aseptic meningitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)

	Nivolumab monotherapy
Blood and lymphatic system disorders	
Very common	lymphopaenia[b], anaemia[b,i], leucopoenia[b], neutropaenia[a,b], thrombocytopaenia[b]
Uncommon	eosinophilia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis
Not known	solid organ transplant rejection[f]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency[j], hypopituitarism, hypophysitis, diabetes mellitus
Rare	diabetic ketoacidosis, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia[b]
Common	dehydration, weight decreased, hypoglycaemia[b]
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome[g]
Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,k], optic neuritis
Not known	myelitis (including transverse myelitis)
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Not known	Vogt-Koyanagi-Harada syndrome[f]
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis[a], pericardial disorders[h], arrhythmia (including ventricular arrhythmia)
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnoea[a], cough
Common	pneumonitis[a], pleural effusion
Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis[a], stomatitis, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer, pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders	
Uncommon	hepatitis, cholestasis

	Nivolumab monotherapy
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	psoriasis, rosacea, erythema multiforme, urticaria
Rare	toxic epidermal necrolysis[a, d], Stevens-Johnson syndrome[a]
Not known	lichen sclerosus[g], other lichen disorders
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e], arthralgia
Common	arthritis
Uncommon	polymyalgia rheumatica
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,], rhabdomyolysis[a,d]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a]
Rare	tubulointerstitial nephritis, cystitis noninfective
General disorders and administration site conditions	
Very common	fatigue, pyrexia
Common	pain, chest pain, oedema[l]
Investigations[b]	
Very common	increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypercalcaemia
Common	increased total bilirubin, hypernatraemia, hypermagnesaemia

Adverse reaction frequencies presented in Table 8 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease.

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

[c] Rash is a composite term which includes rash maculopapular, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash vesicular, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

[d] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.

[f] Post-marketing event (also see section 4.4).

[g] Reported in clinical studies and in the post-marketing setting.

[h] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.

[i] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.

[j] Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency.

[k] Includes encephalitis and limbic encephalitis.

[l] Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling.

Nivolumab in combination with other therapeutic agents (see section 4.2)

Summary of the safety profile

When nivolumab is administered in combination, refer to the SmPC for the other therapeutic agents for additional information on the safety profile, prior to initiation of treatment.

Nivolumab in combination with ipilimumab (with or without chemotherapy)

In the pooled dataset of nivolumab administered in combination with ipilimumab (with or without chemotherapy) across tumour types (n = 2626) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (47%), diarrhoea (35%), rash (37%), nausea

(27%), pruritus (29%), musculoskeletal pain (26%), pyrexia (23%), decreased appetite (22%), cough (21%), abdominal pain (18%), vomiting (18%), constipation (18%), arthralgia (18%), dyspnoea (17%), hypothyroidism (16%), headache (15%), upper respiratory tract infection (13%), oedema (13%), and dizziness (10%). The incidence of Grade 3-5 adverse reactions was 66% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 1.0% fatal adverse reactions attributed to study drug. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%), pyrexia (36%), and headache (26%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy for NSCLC, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate.

Nivolumab in combination with chemotherapy
In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n = 1800), with a minimum follow-up ranging from 7.4 to 23.6 months, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥ 10%) were nausea (48%), fatigue (40%), peripheral neuropathy (33%), decreased appetite (31%), constipation (31%), diarrhoea (28%), vomiting (24%), rash (19%), abdominal pain (18%), stomatitis (18%), musculoskeletal pain (18%), pyrexia (16%), cough (13%), oedema (including peripheral oedema) (12%), and pruritus (11%). Incidences of Grade 3-5 adverse reactions were 69% for nivolumab in combination with chemotherapy, with 1.2% fatal adverse reactions attributed to nivolumab in combination with chemotherapy. Median duration of therapy was 6.14 months (95% CI: 5.78, 6.60) for nivolumab in combination with chemotherapy. For resectable NSCLC, ninety-three percent (93%) of patients received 3 cycles of nivolumab in combination with chemotherapy.

Nivolumab in combination with cabozantinib

In the dataset of nivolumab 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n =320), with a minimum follow -up of 16.0 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), -palmar plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysgeusia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The incidence of Grade 3-5 adverse reactions was 78%, with 0.3% fatal adverse reactions attributed to study drug.

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy) (n = 2626), nivolumab in combination with chemotherapy (n = 1800), and nivolumab in combination with cabozantinib (n = 320) are presented in Table 9. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 9: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	**Combination with chemotherapy**	**Combination with cabozantinib**
Infections and infestations			
Very common	upper respiratory tract infection		upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis	upper respiratory tract infection, pneumonia[a]	pneumonia
Rare	aseptic meningitis		
Blood and lymphatic system disorders			
Very common	anaemia[b,j], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]	neutropaenia[b], anaemia[b,j], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]	anaemia[b], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]
Common	eosinophilia	febrile neutropaenia[a]	eosinophilia
Uncommon	febrile neutropaenia	eosinophilia	
Not known	haemophagocytic lymphohistiocytosis		
Immune system disorders			
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity, infusion related reaction (including cytokine release syndrome)	hypersensitivity (including anaphylactic reaction)
Uncommon			infusion related hypersensitivity reaction
Rare	sarcoidosis		
Not known	solid organ transplant rejection[g]		
Endocrine disorders			
Very common	hypothyroidism		hypothyroidism, hyperthyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus	hypothyroidism, hyperthyroidism, diabetes mellitus	adrenal insufficiency
Uncommon	diabetic ketoacidosis	adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis	hypophysitis, thyroiditis
Rare	hypoparathyroidism		

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Metabolism and nutrition disorders			
Very common	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hypoglycaemia[b], hyperglycaemia[b], weight decreased
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased	hypoalbuminaemia, hypophosphataemia	dehydration
Uncommon	metabolic acidosis		
Rare		tumour lysis syndrome	
Not known	tumour lysis syndrome[h]		
Nervous system disorders			
Very common	headache	peripheral neuropathy	dysgeusia, dizziness, headache
Common	dizziness, peripheral neuropathy	paraesthesia, dizziness, headache	peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis	Guillain-Barré syndrome	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis), optic neuritis	encephalitis	
Not known		myelitis (including transverse myelitis), optic neuritis	
Ear and labyrinth disorders			
Common			tinnitus
Eye disorders			
Common	blurred vision, dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt Koyanagi Harada syndrome		
Cardiac disorders			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia	myocarditis	myocarditis
Not known	pericardial disorders[i]		
Vascular disorders			
Very common			hypertension
Common	hypertension	thrombosis[a, k], hypertension, vasculitis	thrombosis[k]

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Respiratory, thoracic and mediastinal disorders			
Very common	cough, dyspnoea	cough	dysphonia, dyspnoea, cough
Common	pneumonitis[a], pulmonary embolism[a], pleural effusion	pneumonitis[a], dyspnoea	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders			
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation	diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis[a], pancreatitis, stomatitis, gastritis, dry mouth	colitis, dry mouth	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	duodenitis	pancreatitis	pancreatitis, small intestine perforation[a], glossodynia
Rare	intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease		
Not known		pancreatic exocrine insufficiency, coeliac disease	pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders			
Common	hepatitis		hepatitis
Uncommon		hepatitis	
Skin and subcutaneous tissue disorders			
Very common	rash[c], pruritus	rash[c], pruritus	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema,	palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, hair colour change
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders[d]		psoriasis, urticaria
Rare	toxic epidermal necrolysis[a,e] , lichen sclerosus		
Not known			lichen sclerosus, other lichen disorders

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[f], arthralgia	musculoskeletal pain[f]	musculoskeletal pain[f], arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]		
Renal and urinary disorders			
Very common			proteinuria
Common	renal failure (including acute kidney injury)[a]	renal failure[a]	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective[h]
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain
Investigations			
Very common	increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b], hypokalaemia[b], hypercalcaemia[b], hypocalcaemia[b]	hypocalcaemia[b], increased AST[b], increased ALT[b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]	increased alkaline phosphatase[b], increased ALT[b], increased AST[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hypokalaemia[b], hypomagnesaemia[b], hyponatraemia[b], hypocalcaemia[b], hypercalcaemia[b], hypophosphataemia[b], hyperkalaemia[b], hypermagnesaemia[b], hypernatraemia[b]
Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b]	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 9 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

[c] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, nodular rash, and pemphigoid.

[d] Lichen disorders is a composite term which includes lichen keratosis and lichen planus.
[e] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
[f] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.
[g] Post-marketing event (also see section 4.4).
[h] Reported in clinical studies and in the post-marketing setting.
[i] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.
[j] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.
[k] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, limb venous thrombosis.

Description of selected adverse reactions

Nivolumab or nivolumab in combination with other therapeutic agents is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment generally was required in a greater proportion of patients receiving nivolumab in combination with other agents than in those receiving nivolumab monotherapy. Table 10 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 10 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

Table 10: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy, nivolumab in combination with ipilimumab (with or without chemotherapy), nivolumab in combination with chemotherapy, or nivolumab in combination with cabozantinib)

	Nivolumab monotherapy %	Nivolumab in combination with ipilimumab (with or without chemotherapy) %	Nivolumab in combination with chemotherapy %	Nivolumab in combination with cabozantinib %
Immune-related adverse reaction leading to permanent discontinuation				
Pneumonitis	1.4	2.1	2.0	2.5
Colitis	1.2	6	1.8	2.5
Hepatitis	1.1	5	0.7	4.1
Nephritis and renal dysfunction	0.3	1.1	3.1	0.6
Endocrinopathies	0.5	2.2	0.6	1.3
Skin	0.8	1.0	0.9	2.2
Hypersensitivity/Infusion reaction	0.1	0.3	1.7	0

	Nivolumab monotherapy %	Nivolumab in combination with ipilimumab (with or without chemotherapy) %	Nivolumab in combination with chemotherapy %	Nivolumab in combination with cabozantinib %
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]				
Pneumonitis	65	59	59	56
Colitis	14	32	9	8
Hepatitis	21	39	7	23
Nephritis and renal dysfunction	22	27	9	9
Endocrinopathies	5	18	4.3	4.2
Skin	3.3	8	6	8
Hypersensitivity/Infusion reaction	18	18	22	0

[a] at least 40 mg daily prednisone equivalents

[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.3% (155/4646). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (42/4646) and 1.7% (77/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (33/4646) and <0.1% (1/4646) of patients respectively. Six patients (0.1%) had a fatal outcome. Median time to onset was 15.1 weeks (range: 0.7-85.1). Resolution occurred in 107 patients (69.0%) with a median time to resolution of 6.7 weeks (range: 0.1^{+}-109.1^{+}); $^{+}$ denotes a censored observation.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease, was 6.0% (157/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 3.0% (78/2626), 1.0% (27/2626), and 0.3% (8/2626) of patients, respectively. Four patients (0.2%) had a fatal outcome. Median time to onset was 2.7 months (range: 0.1-56.8). Resolution occurred in 129 patients (82.2%) with a median time to resolution of 6.1 weeks (range: 0.1^{+}-149.3^{+}).

In patients treated with nivolumab in combination with chemotherapy, the incidence of pneumonitis including interstitial lung disease was 4.4% (80/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (40/1800), 0.9% (17/1800), and 0.2% (3/1800), of patients, respectively. Three patients (0.2%) had a fatal outcome. Median time to onset was 24.6 weeks (range: 0.6-96.9). Resolution occurred in 58 patients (72.5%) with a median time to resolution of 10.4 weeks (range: 0.3^{+}-171.4^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320) of patients, respectively. Median time to onset was 26.9 weeks (range: 12.3-74.3 weeks). Resolution occurred in 14 patients (77.8%) with a median time to resolution of 7.5 weeks (range: 2.1-60.7^{+} weeks).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 15.4% (716/4646). The majority of cases were Grade 1 or 2 in severity reported in 9.9% (462/4646) and 4.0% (186/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (67/4646) and <0.1% (1/4646) of patients respectively. Median time to onset was 8.3 weeks (range: 0.1-115.6). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1-124.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 26.0% (682/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 8.1% (212/2626), 6.4% (167/2626), and 0.2% (4/2626), of patients, respectively. Two patients (<0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 618 patients (91%) with a median time to resolution of 2.9 weeks (range: 0.1-170.0[+]). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of diarrhoea or colitis was 46.7%, including Grade 2 (13.6%), Grade 3 (15.8%), and Grade 4 (0.4%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of diarrhoea or colitis was 22.5% (405/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 7.2% (130/1800), 3.1% (56/1800), and 0.3% (6/1800) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 4.4 weeks (range: 0.1-93.6). Resolution occurred in 357 patients (88.6%) with a median time to resolution of 1.6 weeks (range: 0.1-212.3[+]).

In patients treated with nivolumab in combination with cabozantinib, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). Median time to onset was 12.9 weeks (range: 0.3-110.9 weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7[+] weeks).

Immune-related hepatitis
In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 8.0% (371/4646). The majority of cases were Grade 1 or 2 in severity reported in 4.3% (200/4646) and 1.8% (82/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (74/4646) and 0.3% (15/4646) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-132.0). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4[+]).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of liver function test abnormalities was 21.2% (556/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 5.0% (132/2626), 8.3% (218/2626), and 1.3% (34/2626) of patients, respectively. Seven patients (0.3%) had a fatal outcome. Median time to onset was 1.5 months (range: 0.0-36.6). Resolution occurred in 482 patients (87.0%) with a median time to resolution of 5.9 weeks (range: 0.1-175.9[+]). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of liver function test abnormalities was 30.1% including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for HCC, the incidence of liver function test abnormalities was 34.3% including Grade 2 (8.4%), Grade 3 (14.2%), and Grade 4 (2.7%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of liver function test abnormalities was 18% (322/1800). Grade 2, Grade 3 and Grade 4 cases were reported in 5.1% (92/1800), 2.6% (47/1800) and < 0.1% (1/1800) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-99.0). Resolution occurred in 258 patients (81.1%) with a median time to resolution of 7.4 weeks (range: 0.4-240.0[+]).

In patients treated with nivolumab in combination with cabozantinib, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. Median time to onset was 8.3 weeks (range: 0.1-107.9 weeks). Resolution occurred in 101 patients (75.9%) with a median time to resolution of 9.6 weeks (range: 0.1-89.3[+] weeks).

Immune-related nephritis and renal dysfunction
In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.6% (121/4646). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (69/4646) and 0.7% (32/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (18/4646) and <0.1% (2/4646) of patients, respectively. Median time to onset was 12.1 weeks (range: 0.1-79.1).

Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1[+]).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 5.4% (141/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 2.0% (52/2626), 0.8% (21/2626), and 0.4% (11/2626) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.6 months (range: 0.0-34.8). Resolution occurred in 110 patients (78.0%) with a median time to resolution of 5.9 weeks (range: 0.1-172.1[+]).

In patients treated with nivolumab in combination with chemotherapy, the incidence of nephritis or renal dysfunction was 10.9% (196/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 3.7% (66/1800), 1.4% (25/1800), and 0.2% (3/1800) of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 6.7 weeks (range: 0.1-60.7). Resolution occurred in 133 patients (67.9%) with a median time to resolution of 9.1 weeks (range: 0.1-226.0[+]).

In patients treated with nivolumab in combination with cabozantinib, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. Median time to onset was 14.2 weeks (range: 2.1-87.1 weeks). Resolution occurred in 18 patients (58.1%) with a median time to resolution of 10.1 weeks (range: 0.6-90.9[+] weeks).

Immune-related endocrinopathies
In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 13.0% (603/4646). The majority of cases were Grade 1 or 2 in severity reported in 6.6% (305/4646) and 6.2% (290/4646) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4646) of patients. Hypophysitis (3 Grade 1, 7 Grade 2, 9 Grade 3, and 1 Grade 4), hypopituitarism (6 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute and blood corticotrophin decreased) (2 Grade 1, 23 Grade 2, and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade 1, 3 Grade 2 and 8 Grade 3 and 2 Grade 4), were reported. Median time to onset of these endocrinopathies was 11.1 weeks (range: 0.1-126.7). Resolution occurred in 323 patients (48.7%). Median time to resolution was 48.6 weeks (range: 0.4-204.4[+]).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 23.2% (608/2626). Grade 2 and Grade 3 thyroid disorders were reported in 12.7% (333/2626) and 1.0% (27/2626) of patients, respectively.
Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 1.9% (49/2626) and 1.5% (40/2626) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.6% (16/2626) and 0.5% (13/2626) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute, blood corticotrophin decreased and immune-mediated adrenal insufficiency) occurred in 2.7% (72/2626), 1.6% (43/2626) and 0.2% (4/2626) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in < 0.1% (1/2626), 0.3% (8/2626), 0.3% (7/2626), and 0.2% (6/2626) of patients, respectively. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 297 patients (40.0%). Time to resolution ranged from 0.3 to 257.1[+] weeks.

In patients treated with nivolumab in combination with chemotherapy, the incidence of thyroid disorders was 12.8% (230/1800). Grade 2 and Grade 3 thyroid disorders were reported in 6.3% (114/1800) and 0.1% (2/1800) of patients, respectively. Grade 3 hypophysitis occurred in 0.1% (2/1800) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (4/1800) of patients, each. Grade 2, Grade 3, and Grade 4 adrenal insufficiency occurred in 0.6% (11/1800), 0.2% (3/1800), and < 0.1% (1/1800) of patients, respectively. One patient (< 0.1%) had a fatal outcome due to adrenal insufficiency. Diabetes mellitus including Type 1 diabetes mellitus and fulminant Type 1 diabetes mellitus (4 Grade 2, 2 Grade 3, and 1 Grade 4), and diabetic ketoacidosis (1 Grade 2 and 1 Grade 4)

were reported. Median time to onset of these endocrinopathies was 15.3 weeks (range: 1.1-124.3). Resolution occurred in 101 patients (40.1%). Time to resolution ranged from 0.3^{+} to 233.6^{+} weeks.

In patients treated with nivolumab in combination with cabozantinib, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. Median time to onset of these endocrinopathies was 12.3 weeks (range: 2.0-89.7 weeks). Resolution occurred in 50 patients (35.2%). Time to resolution ranged from 0.9 to 132.0^{+} weeks.

Immune-related skin adverse reactions
In patients treated with nivolumab monotherapy, the incidence of rash was 30.0% (1396/4646). The majority of cases were Grade 1 in severity reported in 22.8% (1060/4646) of patients. Grade 2 and Grade 3 cases were reported in 5.9% (274/4646) and 1.3% (62/4646) of patients respectively. Median time to onset was 6.7 weeks (range: 0.1-121.1). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (0.1-192.7^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of rash was 46.1% (1210/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 14.3% (375/2626), 4.6% (120/2626), and 0.1% (3/2626) of patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 843 patients (70%) with a median time to resolution of 12.1 weeks (range: 0.1-268.7^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of rash was 25.4% (457/1800). Grade 2 and Grade 3 cases were reported in 6.2% (111/1800) and 2.3% (42/1800) of patients, respectively. Median time to onset was 6.4 weeks (range: 0.1-97.4). Resolution occurred in 320 patients (70.2%) with a median time to resolution of 12.1 weeks (range: 0.1-258.7^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. Median time to onset was 6.14 weeks (range: 0.1-104.4 weeks). Resolution occurred in 137 patients (68.2%) with a median time to resolution of 18.1 weeks (range: 0.1-130.6^{+} weeks).

Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4).

Infusion reactions
In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.0% (188/4646), including 9 Grade 3 and 3 Grade 4 cases.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.5% (118/2626). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 1.9% (49/2626), 2.4% (62/2626), 0.2% (6/2626), and < 0.1% (1/2626) of patients, respectively. Among patients with MPM treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

In patients treated with nivolumab in combination with chemotherapy, the incidence of hypersensitivity/infusion reactions was 8.2% (148/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 4.6% (83/1800), 1.1% (20/1800), and 0.2% (3/1800) of patients, respectively.

In patients treated with nivolumab in combination with cabozantinib, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients.

Complications of allogeneic HSCT in classical Hodgkin lymphoma
Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT (see section 4.4).
In 62 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 17/62 patients (27.4%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in four patients (6%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation. Steroids were used in four patients and three patients responded to steroids. Hepatic veno-occlusive disease occurred in two patients, one of whom died of GVHD and multi-organ failure. Nineteen of 62 patients (30.6%) died from complications of allogeneic HSCT after nivolumab. The 62 patients had a median follow-up from subsequent allogeneic HSCT of 38.5 months (range: 0-68 months).

Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC
In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to nivolumab monotherapy in patients with advanced RCC. In patients with Grade ≥ 2 increased ALT or AST (n=85): median time to onset was 10.1 weeks (range: 2.0 to 106.6 weeks), 26% received corticosteroids for median duration of 1.4 weeks (range: 0.9 to 75.3 weeks), and resolution to Grades 0-1 occurred in 91% with median time to resolution of 2.3 weeks (range: 0.4 to 108.1^{+} weeks). Among the 45 patients with Grade ≥ 2 increased ALT or AST who were rechallenged with either nivolumab (n=10) or cabozantinib (n=10) administered as a single agent or with both (n=25), recurrence of Grade ≥ 2 increased ALT or AST was observed in 3 patients receiving OPDIVO, 4 patients receiving cabozantinib, and 8 patients receiving both OPDIVO and cabozantinib.

Laboratory abnormalities
In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.4% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.7% for leucopoenia, 8.7% for lymphopaenia, 0.9% for neutropaenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.3% for increased ALT, 0.8% for increased total bilirubin, 0.7% for increased creatinine, 2.0% for hyperglycaemia, 0.7% for hypoglycaemia, 3.8% for increased amylase, 6.9% for increased lipase, 4.7% for hyponatraemia, 1.6% for hyperkalaemia, 1.3% for hypokalaemia, 1.1% for hypercalcaemia, 0.6% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.6% for hypocalcaemia, 0.6% for hypoalbuminaemia, and <0.1% for hypernatraemia.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.8% for anaemia, 1.8% for thrombocytopaenia, 2.2% for leucopoenia, 6.9% for lymphopaenia, 3.3% for neutropaenia, 2.7% for increased alkaline phosphatase, 9.8% for increased AST, 9.3% for increased ALT, 2.3% for increased total bilirubin, 1.8% for increased creatinine, 1.4% for hypoalbuminaemia, 7.1% for hyperglycaemia, 0.7% for hypoglycaemia, 7.8% for increased amylase, 16.3% for increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 0.8% for hypercalcaemia, 2.0% for hyperkalaemia, 0.8% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.0% for hypokalaemia, and 8.7% for hyponatraemia.

Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, a higher proportion of patients experienced a worsening from baseline to Grade 3 or 4 increased ALT (15.3%).

In patients treated with nivolumab in combination with chemotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows:

14.7% for anaemia, 6.2% for thrombocytopaenia, 11.7% leukopaenia, 13.6% for lymphopaenia, 26.3% neutropaenia, 2.0% for increased alkaline phosphatase, 3.3% for increased AST, 2.6% for increased ALT, 1.9% for increased bilirubin, 1.3% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.4% for hypernatraemia, 8.1% for hyponatraemia, 1.8% for hyperkalaemia, 5.1% for hypokalaemia, 0.7% for hypercalcaemia, 1.8% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.7% for hyperglycaemia, and 0.6% for hypoglycaemia.

In patients treated with nivolumab in combination with cabozantinib, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.5% for anaemia (all Grade 3), 0.3% for thrombocytopaenia, 0.3% for leucopoenia, 7.5% for lymphopaenia, 3.5% for neutropaenia, 3.2% for increased alkaline phosphatase, 8.2% for increased AST, 10.1% for increased ALT, 1.3% for increased total bilirubin, 1.3% for increased creatinine, 11.9% for increased amylase, 15.6% for increased lipase, 3.5% for hyperglycaemia, 0.8% for hypoglycaemia, 2.2% for hypocalcaemia, 0.3% for hypercalcaemia, 5.4% for hyperkalaemia, 4.2% for hypermagnesaemia, 1.9% for hypomagnesaemia 3.2% for hypokalaemia, 12.3% for hyponatraemia, and 21.2% for hypophosphataemia.

Immunogenicity
Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 patients (9.3%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.6%) testing positive for neutralising antibodies.

Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the 1407 patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 7.2% tested positive for treatment emergent anti-product-antibodies with 0.5% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-nivolumab antibodies or neutralising antibodies against nivolumab, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralising antibodies was 2.6%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralising antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and the neutralising antibodies was 1.6%.

Although the clearance of nivolumab was increased by 20% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination.

Paediatric population

The safety of nivolumab as monotherapy (3 mg/kg every 2 weeks) and in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in

97 paediatric patients aged ≥ 1 year to < 18 years (including 53 patients 12 to < 18 years) with recurrent or refractory solid or haematological tumours, including advanced melanoma, in clinical study CA209070. The safety profile in paediatric patients was generally similar to that seen in adults treated with nivolumab as monotherapy or in combination with ipilimumab. No new safety signals were observed. Long-term safety data is unavailable on the use of nivolumab in adolescents 12 years of age and older.

The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab monotherapy were fatigue (35.9%) and decreased appetite (21.9%). The majority of adverse reactions reported for nivolumab monotherapy were Grade 1 or 2 in severity. Twenty-one patients (33%) had one or more Grades 3 to 4 adverse reactions.

The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab in combination with ipilimumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for nivolumab in combination with ipilimumab were Grade 1 or 2 in severity. Ten patients (30%) had one or more Grades 3 to 4 adverse reactions.

No new safety signals were observed in clinical study CA209908 of 151 paediatric patients with high-grade primary central nervous system (CNS) malignancies (see section 5.1), relative to data available in adult studies across indications.

Elderly

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see section 5.1). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1). In MPM patients, there was a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively). In HCC patients there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received nivolumab with ipilimumab (53% and 27%, respectively).

For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1).

Hepatic or renal impairment

In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/ death ligand 1) inhibitors. ATC code: L01FF01.

Mechanism of action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

Clinical efficacy and safety

Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks. Additionally, based on these relationships, there were no clinically significant differences between a nivolumab dose of 480 mg every 4 weeks or 3 mg/kg every 2 weeks in adjuvant treatment of melanoma, advanced melanoma and advanced RCC.

Melanoma

Treatment of advanced melanoma

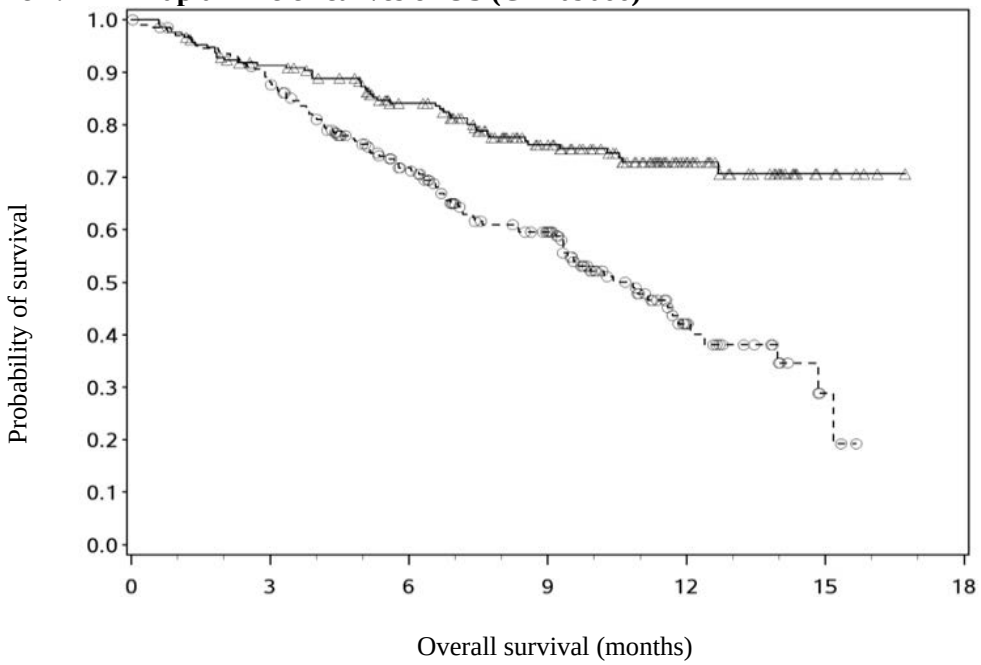
Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an ECOG performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m^2 every 3 weeks. Randomisation was stratified by tumour PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse events with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and objective response rate (ORR).

Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma (≥ 5% tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

The Kaplan-Meier curves for OS are shown in Figure 1.

Figure 1: Kaplan-Meier curves of OS (CA209066)



Number of subjects at risk

Nivolumab						
210	185	150	105	45	8	0
Dacarbazine						
208	177	123	82	22	3	0

—△—— Nivolumab (events: 50/210), median and 95% CI: N.A.
- - -❍- - - Dacarbazine (events: 96/208), median and 95% CI: 10.84 (9.33, 12.09)

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%).

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Efficacy results are shown in Table 11.

Table 11: Efficacy results (CA209066)

	nivolumab (n = 210)		dacarbazine (n = 208)
Overall survival			
Events	50 (23.8%)		96 (46.2%)
Hazard ratio		0.42	
99.79% CI		(0.25, 0.73)	
95% CI		(0.30, 0.60)	
p-value		< 0.0001	
Median (95% CI)	Not reached		10.8 (9.33, 12.09)
Rate (95% CI)			
At 6 months	84.1 (78.3, 88.5)		71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)		42.1 (33.0, 50.9)
Progression-free survival			
Events	108 (51.4%)		163 (78.4%)
Hazard ratio		0.43	
95% CI		(0.34, 0.56)	
p-value		< 0.0001	
Median (95% CI)	5.1 (3.48, 10.81)		2.2 (2.10, 2.40)
Rate (95% CI)			
At 6 months	48.0 (40.8, 54.9)		18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)		NA
Objective response	84 (40.0%)		29 (13.9%)
(95% CI)	(33.3, 47.0)		(9.5, 19.4)
Odds ratio (95% CI)		4.06 (2.52, 6.54)	
p-value		< 0.0001	
Complete response (CR)	16 (7.6%)		2 (1.0%)
Partial response (PR)	68 (32.4%)		27 (13.0%)
Stable disease (SD)	35 (16.7%)		46 (22.1%)
Median duration of response			
Months (range)	Not reached (0^+-12.5^+)		6.0 (1.1-10.0^+)
Median time to response			
Months (range)	2.1 (1.2-7.6)		2.1 (1.8-3.6)

"+" denotes a censored observation.

Randomised phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, open-label study (CA209037). The study included adult patients who had progressed on or after ipilimumab and if BRAF V600 mutation positive had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma, active brain or leptomeningeal metastases or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and tumour PD-L1 status and best response to prior ipilimumab.

The co-primary efficacy outcome measures were confirmed ORR in the first 120 patients treated with nivolumab, as measured by independent radiology review committee (IRRC) using RECIST, version 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and > 2 for 21% of patients. Twenty-two percent of patients had tumours that tested BRAF mutation positive and 50% of patients had tumours that were considered PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. Efficacy results are presented in Table 12.

Table 12: Best overall response, time and duration of response (CA209037)

	nivolumab (n = 120)	**chemotherapy (n = 47)**
Confirmed objective response (IRRC)	38 (31.7%)	5 (10.6%)
(95% CI)	(23.5, 40.8)	(3.5, 23.1)
Complete response (CR)	4 (3.3%)	0
Partial response (PR)	34 (28.3%)	5 (10.6%)
Stable disease (SD)	28 (23.3%)	16 (34.0%)
Median duration of response		
Months (range)	Not reached	3.6 (Not available)
Median time to response		
Months (range)	2.1 (1.6-7.4)	3.5 (2.1-6.1)

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Updated analysis (24-month follow-up)
Among all randomised patients, the ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median durations of response were 31.9 months (range: 1.4$^+$-31.9) and 12.8 months (range: 1.3$^+$-13.6$^+$), respectively. The PFS HR for nivolumab vs. chemotherapy was 1.03 (95% CI: 0.78, 1.36). The ORR and PFS were assessed by IRRC per RECIST version 1.1.

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with

54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm.

Efficacy by BRAF status: Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. The ORRs in the BRAF mutation-positive subgroup were 17% (95% CI: 8.4, 29.0) for nivolumab and 11% (95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (95% CI: 24.0, 36.7) and 9% (95% CI: 4.6, 16.7), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 1.58 (95% CI: 0.87, 2.87) for BRAF mutation-positive patients and 0.82 (95% CI: 0.60, 1.12) for BRAF wild-type patients. The OS HRs for nivolumab vs. chemotherapy were 1.32 (95% CI: 0.75, 2.32) for BRAF mutation-positive patients and 0.83 (95% CI: 0.62, 1.11) for BRAF wild-type patients.

Efficacy by tumour PD-L1 expression: Objective responses to nivolumab were observed regardless of tumour PD-L1 expression. However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated.

In patients with tumour PD-L1 expression ≥ 1%, ORR was 33.5% for nivolumab (n = 179; 95% CI: 26.7, 40.9) and 13.5% for chemotherapy (n = 74; 95% CI: 6.7, 23.5). In patients with tumour PD-L1 expression <1%, ORR per IRRC was 13.0% (n = 69; 95% CI: 6.1, 23.3) and 12.0% (n = 25; 95% CI: 2.5, 31.2), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 0.76 (95% CI: 0.54, 1.07) in patients with tumour PD-L1 expression ≥ 1% and 1.92 (95% CI: 1.05, 3.5) in patients with tumour PD-L1 expression < 1%.

The OS HRs for nivolumab vs. chemotherapy were 0.69 (95% CI: 0.49, 0.96) in patients with tumour PD-L1 expression ≥ 1% and 1.52 (95% CI: 0.89, 2.57) in patients with tumour PD-L1 expression < 1%.

These subgroup analyses should be interpreted with caution given the small size of the subgroups and lack of statistically significant difference in OS in the all randomised population.

Open-label phase 1 dose-escalation study (MDX1106-03)
The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma. Of the 306 previously treated patients enrolled in the study, 107 had melanoma and received nivolumab at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg for a maximum of 2 years. In this patient population, objective response was reported in 33 patients (31%) with a median duration of response of 22.9 months (95% CI: 17.0, NR). The median PFS was 3.7 months (95% CI: 1.9, 9.3). The median OS was 17.3 months (95% CI: 12.5, 37.8), and the estimated OS rates were 42% (95% CI: 32, 51) at 3 years, 35% (95% CI: 26, 44) at 4 years, and 34% (95% CI: 25, 43) at 5 years (minimum follow-up of 45 months).

Single-arm phase 2 study (CA209172)
Study CA209172 was a single-arm, open label study of nivolumab monotherapy in patients with stage III (unresectable) or stage IV metastatic melanoma after prior treatment containing an anti-CTLA-4 monoclonal antibody. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 1008 treated patients, 103 (10%) had ocular/uveal melanoma, 66 (7%) had an ECOG performance score of 2, 165 (16%) had asymptomatic treated and untreated CNS metastases, 13 (1.3%) had treated leptomeningeal metastases, 25 (2%) had autoimmune disease, and 84 (8%) had Grade 3-4 immune-related AEs with prior anti-CTLA-4 therapy. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed response rates at week 12 are presented in Table 13 below.

Table 13: Response rate at week 12 - all response evaluable patients and by subgroup (CA209172)

	Total	Ocular/ Uveal melanoma	ECOG PS 2	CNS metastasis	Autoimmune disease	Grade 3-4 irAEs with anti-CTLA-4
N	161/588	4/61	4/20	20/73	3/16	13/46
(%)[a]	(27.4)	(6.6)	(20.0)	(27.4)	(18.8)	(28.3)

[a] Responses were assessed per RECIST 1.1 for 588/1008 (58.3%) of patients who continued treatment through week 12 and had a follow-up scan at week 12.

Randomised phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy vs. ipilimumab as monotherapy (CA209067)

The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg or nivolumab 3 mg/kg vs. ipilimumab 3 mg/kg monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209067). The differences between the two nivolumab-containing groups were evaluated descriptively. The study included adult patients with confirmed unresectable Stage III or Stage IV melanoma. Patients were to have ECOG performance status score of 0 or 1. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled. Prior adjuvant or neoadjuvant therapy was allowed if it was completed at least 6 weeks prior to randomisation. Patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases were excluded from the study.

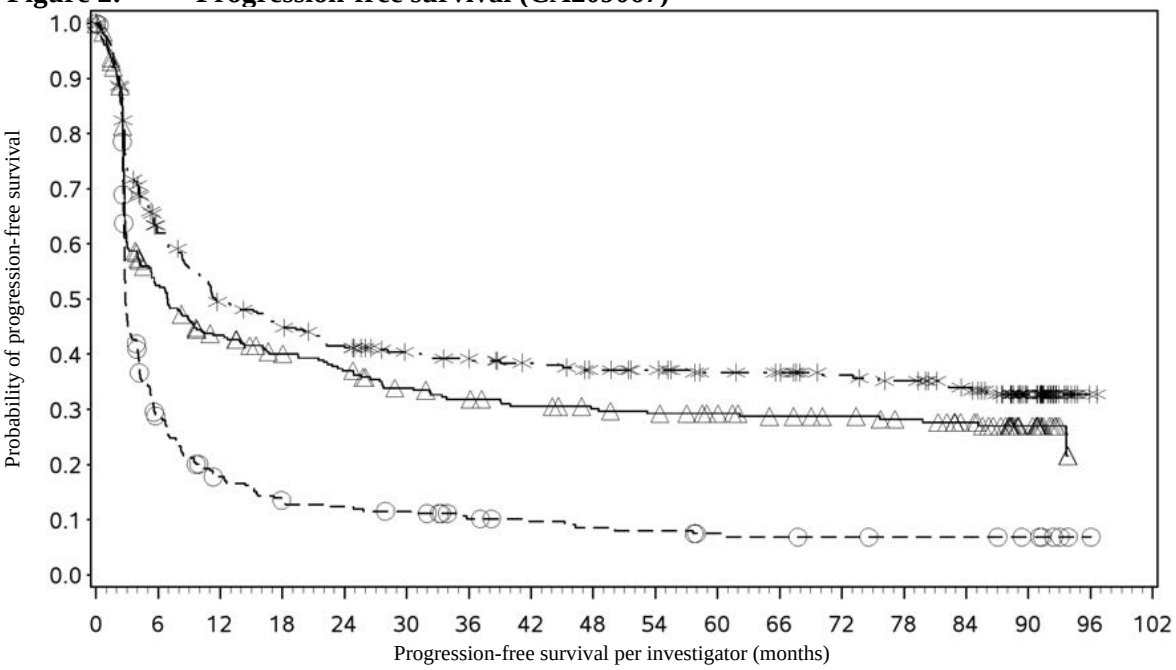
A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomisation was stratified by PD-L1 expression (≥ 5% vs. < 5% tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted 12 weeks after randomisation then every 6 weeks for the first year, and every 12 weeks thereafter. The primary outcome measures were progression-free survival and OS. ORR and the duration of response were also assessed.

Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18 to 90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy. Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1 ≥ 5% tumour cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the three treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

At primary analysis (minimum follow-up 9 months) the median PFS was 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR = 0.57, 99.5% CI: 0.43, 0.76; $p < 0.0001$). The median PFS was 11.5 months in the nivolumab in combination with ipilimumab group, as compared with 2.9 months in the ipilimumab group (HR = 0.42, 99.5% CI: 0.31, 0.57; $p < 0.0001$).

PFS results from descriptive analysis (with minimum follow up of 90 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

Figure 2: Progression-free survival (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab																	
314	175	138	126	112	103	99	93	87	84	78	76	70	66	57	33	1	-
Nivolumab																	
316	151	120	106	97	84	78	73	69	66	62	57	54	50	44	21	0	-
Ipilimumab																	
315	78	46	34	31	28	21	18	16	15	12	11	10	9	9	7	1	-

- - -✳- - - Nivolumab+ipilimumab (events: 189/314), median and 95% CI: 11.50 (8.90, 20.04).
PFS rate at 12 months and 95% CI: 49% (44, 55), PFS rate at 60 months and 95% CI: 36% (32, 42), PFS rate at 90 months and 95% CI: 33% (27, 39)

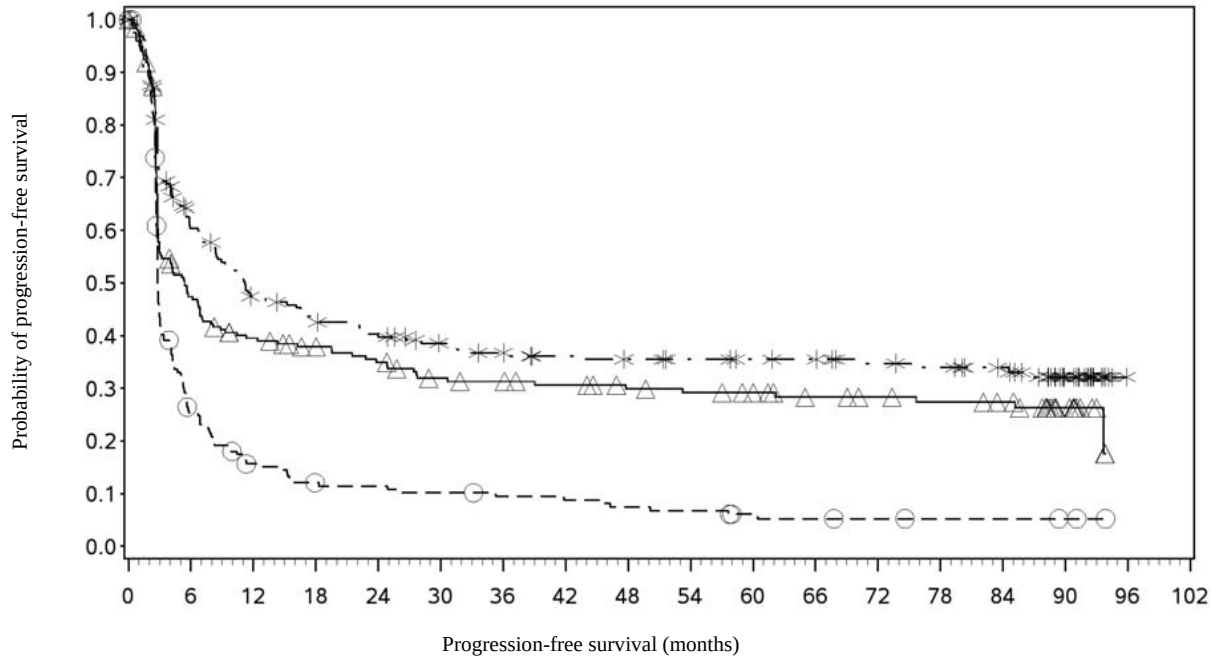
—△— Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)

- - -○- - - Ipilimumab (events: 261/315), median and 95% CI: 2.86 (2.79, 3.09).
PFS rate at 12 months and 95% CI: 18% (14, 23), PFS rate at 60 months and 95% CI: 8% (5, 12), PFS rate at 90 months and 95% CI: 7% (4, 11)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.35, 0.51)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.53 (0.44, 0.64)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.79 (0.65, 0.97)

Figure 3: Progression-free survival by PD-L1 expression: 5% cut off (CA209067)

PD-L1 expression < 5%



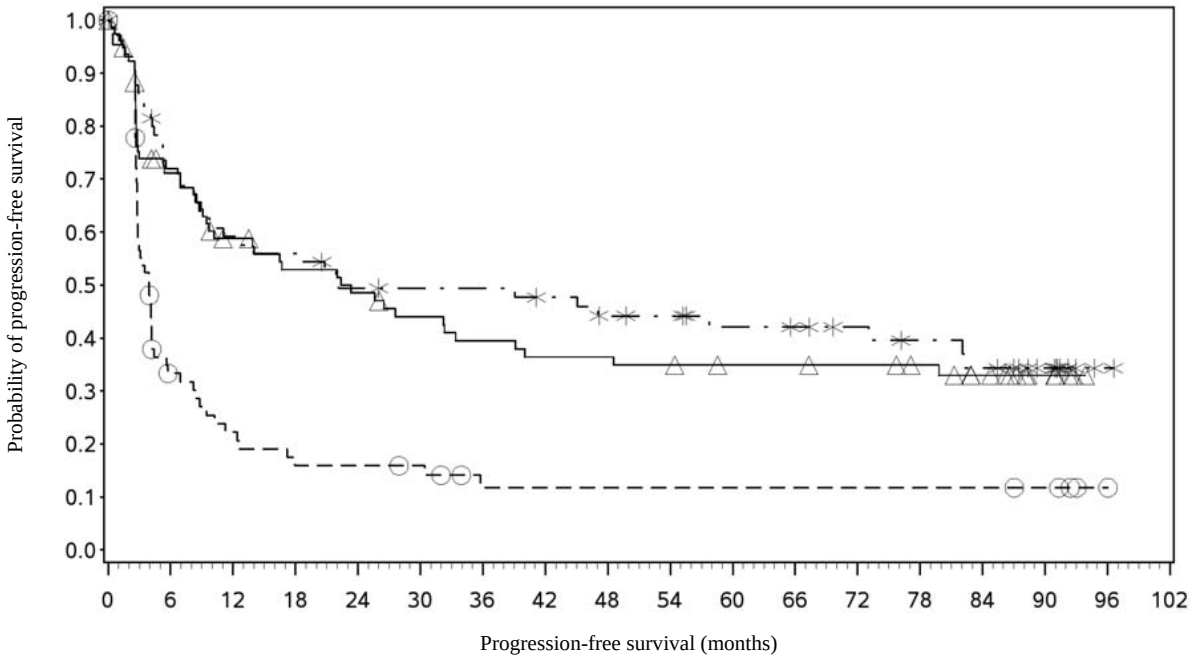
Number of subjects at risk

Nivolumab + ipilimumab																
210	113	87	78	71	64	60	56	54	52	50	49	45	43	39	22	0	-
Nivolumab																
208	91	73	66	60	51	49	46	42	40	38	33	31	29	27	12	0	-
Ipilimumab																
202	45	26	19	18	16	14	13	11	10	7	6	5	4	4	3	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 127/210), median and 95% CI: 11.17 (7.98, 17.51)
—△—— Nivolumab (events: 139/208), median and 95% CI: 5.39 (2.96, 7.13)
- - -❍- - - Ipilimumab (events: 171/202), median and 95% CI: 2.79 (2.76, 3.02)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.33, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.54 (0.43, 0.68)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.77 (0.61, 0.98)

PD-L1 expression ≥ 5%



Number of subjects at risk

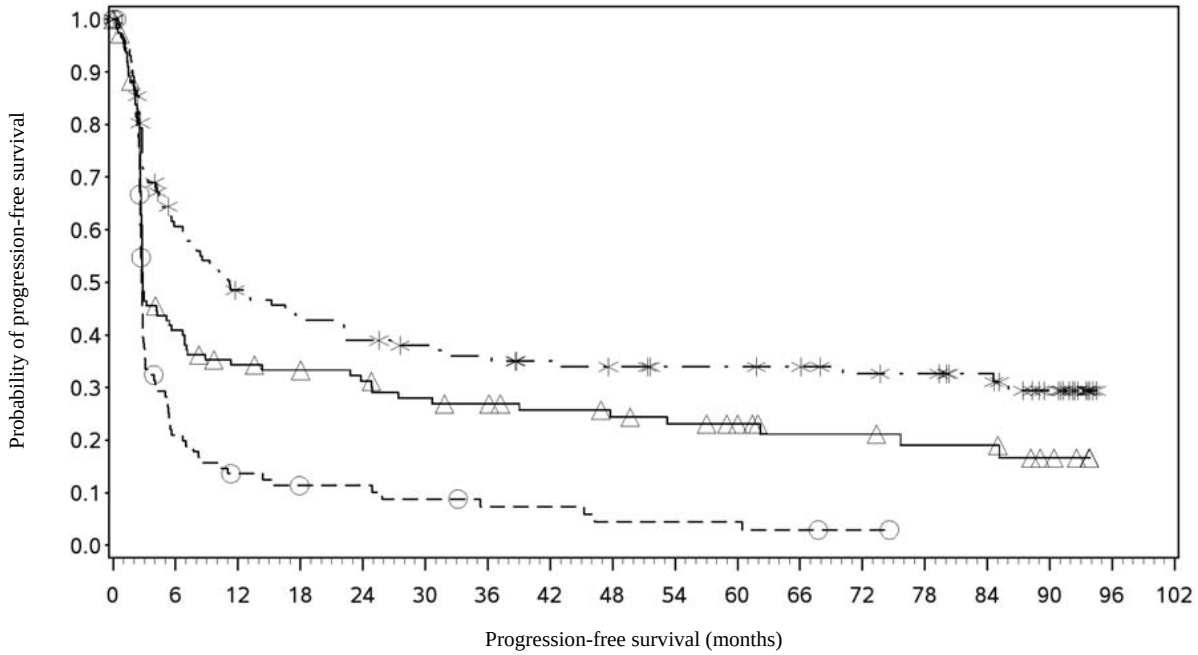
Nivolumab + ipilimumab																	
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1	-
Nivolumab																	
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0	-
Ipilimumab																	
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1	-

- - -✳- - - Nivolumab+ipilimumab (events: 36/68), median and 95% CI: 22.11 (9.72, 82.07)
----△---- Nivolumab (events: 48/80), median and 95% CI: 22.34 (9.46, 39.13)
- - -❍- - - Ipilimumab (events: 60/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.38 (0.25, 0.58)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.43 (0.29, 0.64)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.89 (0.58, 1.35)

Figure 4: Progression-free survival by PD-L1 expression: 1% cut off (CA209067)

PD-L1 expression < 1%



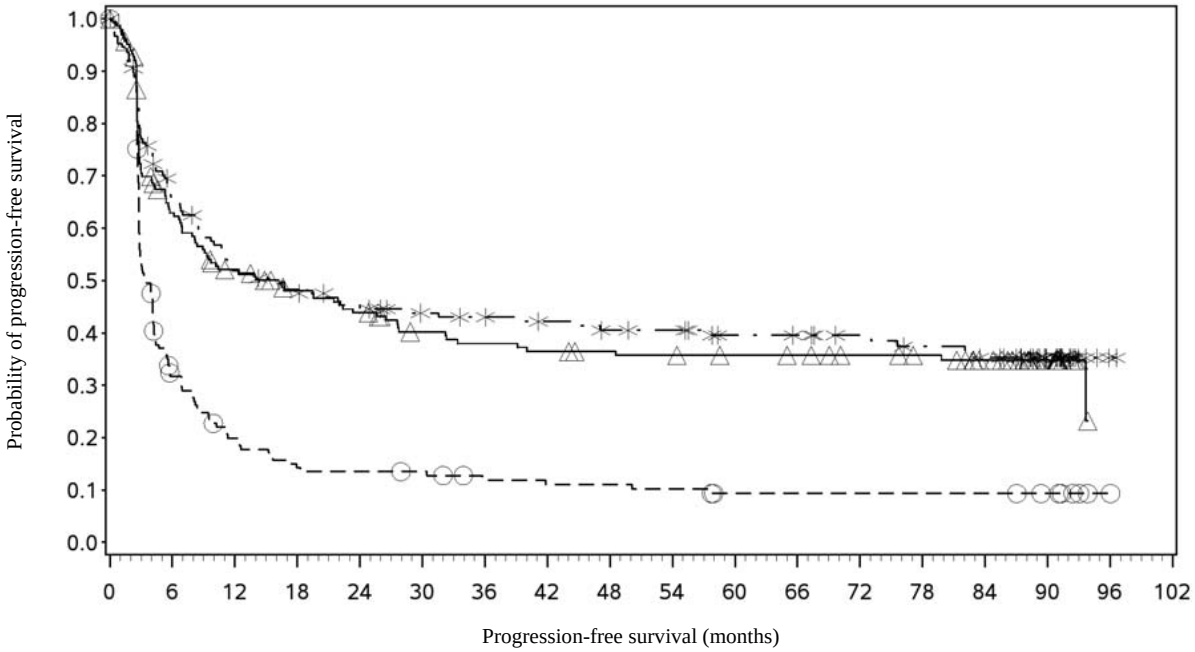
Number of subjects at risk

Nivolumab + ipilimumab																	
123	65	51	46	41	38	36	33	31	29	29	28	25	24	21	13	0	-
Nivolumab																	
117	44	35	33	30	26	24	21	19	17	15	11	11	9	9	5	0	-
Ipilimumab																	
113	20	12	9	9	7	5	5	3	3	3	2	1	0	0	0	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 76/123), median and 95% CI: 11.17 (6.93, 22.18)
—△—— Nivolumab (events: 85/117), median and 95% CI: 2.83 (2.76, 5.62)
- - -O- - - Ipilimumab (events: 94/113), median and 95% CI: 2.73 (2.66, 2.83)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.39 (0.28, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.59 (0.44, 0.79)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.66 (0.48, 0.90)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab + ipilimumab																	
155	93	73	67	60	55	53	50	47	46	41	40	37	34	31	17	1	-
Nivolumab																	
171	99	79	69	63	54	51	49	47	46	44	43	40	38	32	14	0	-
Ipilimumab																	
164	46	28	20	19	18	14	13	13	12	9	9	9	9	9	7	1	-

- - -✳- - - Nivolumab+ipilimumab (events: 90/155), median and 95% CI: 16.13 (8.90, 45.08)
----△---- Nivolumab (events: 102/171), median and 95% CI: 16.20 (8.11, 27.60)
- - -❍- - - Ipilimumab (events: 137/164), median and 95% CI: 3.48 (2.83, 4.17)

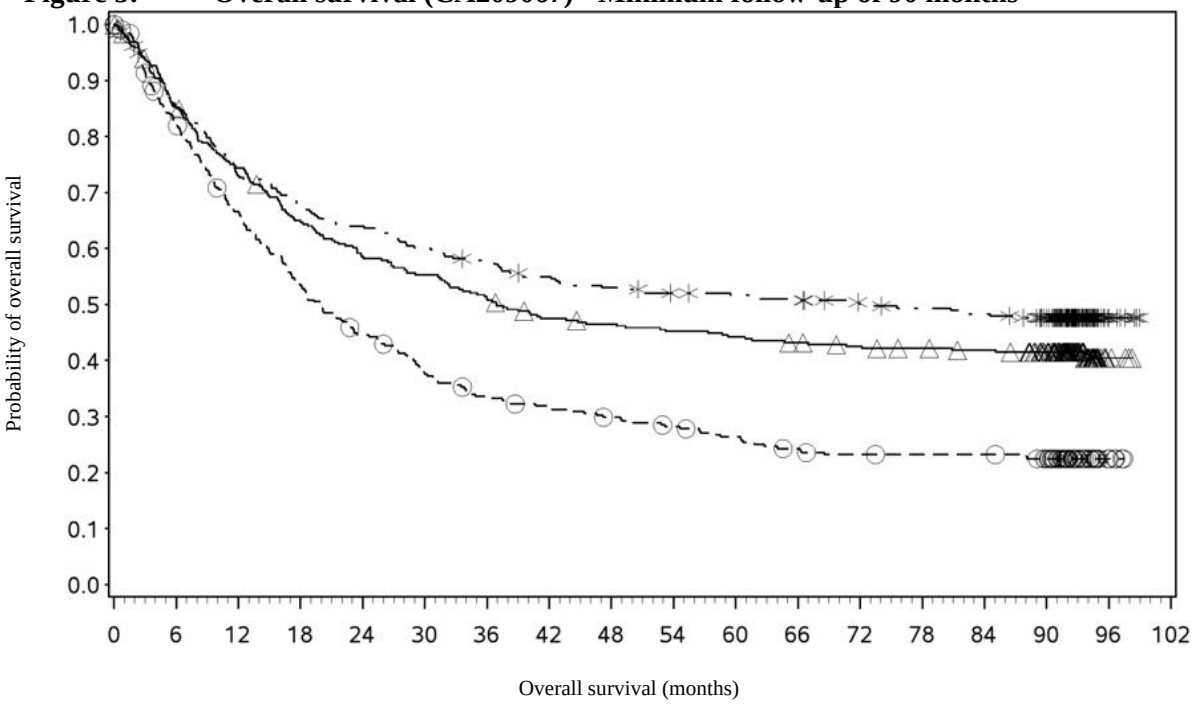
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

The final (primary) OS analysis occurred when all patients had a minimum follow-up of 28 months. At 28 months, median OS was not reached in the nivolumab group as compared with 19.98 months in the ipilimumab group (HR = 0.63, 98% CI: 0.48, 0.81; p-value: < 0.0001). Median OS was not reached in the nivolumab in combination with ipilimumab group as compared with the ipilimumab group (HR = 0.55, 98% CI: 0.42, 0.72; p-value: < 0.0001).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 90 months show outcomes consistent with the original primary analysis. OS results from this follow-up analysis are shown in Figure 5 (all randomised), Figure 6 and 7 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 36.0%, 49.1%, and 66.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 19.1%, 34.2%, and 48.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 5: Overall survival (CA209067) - Minimum follow-up of 90 months



Number of subjects at risk

Nivolumab+ipilimumab																	
314	265	227	210	199	187	179	169	163	158	156	153	147	144	141	129	7	-
Nivolumab																	
316	266	231	201	181	171	158	145	141	137	134	130	126	123	120	107	4	-
Ipilimumab																	
315	253	203	163	135	113	100	94	87	81	75	68	64	63	63	57	5	-

- - -✳- - - Nivolumab+ipilimumab (events: 162/314), median and 95% CI: 72.08 (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), 36 months: 58% (52, 63), 60 months: 52% (46, 57), and 90 months: 48% (42, 53)

—△—— Nivolumab (events: 182/316), median and 95% CI: 36.93 months (28.25, 58.71)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57), 60 months: 44% (39, 50), and 90 months: 42% (36, 47)

- - -❍- - - Ipilimumab (events: 235/315), median and 95% CI: 19.94 months (16.85, 24.61)
OS rate and 95% CI at 12 months: 67% (61, 72), 24 months: 45% (39, 50), 36 months: 34% (29, 39), 60 months: 26% (22, 31), and 90 months: 22% (18, 27)

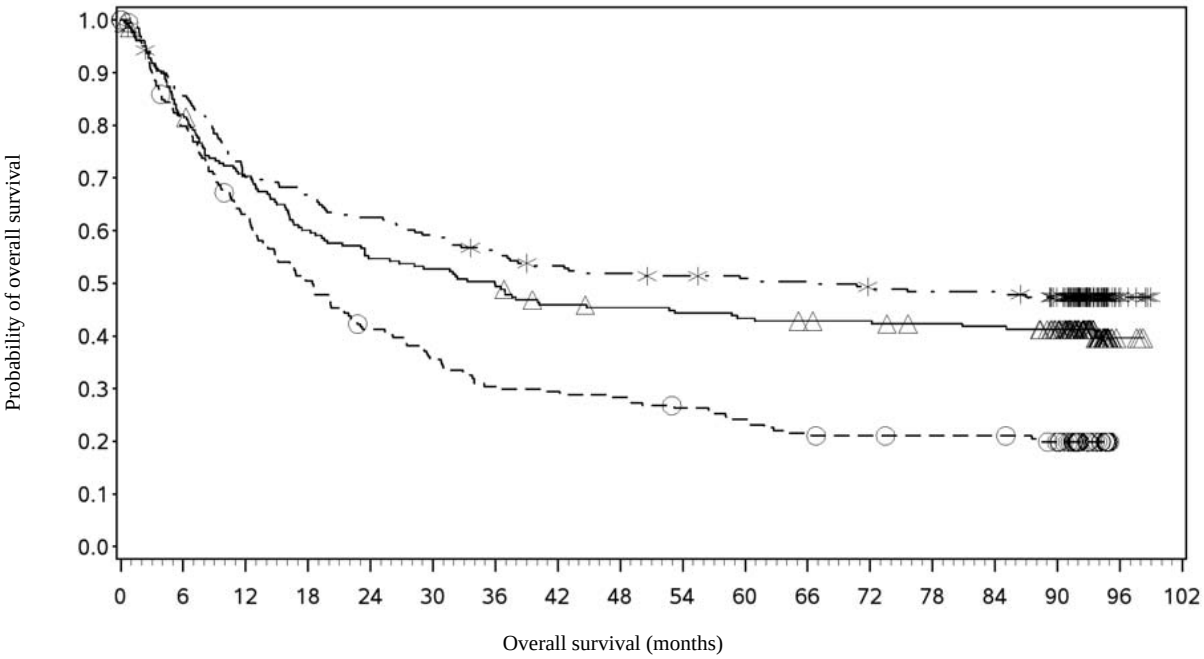
Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65)

Nivolumab vs ipilimumab - HR (95% CI): 0.63 (0.52, 0.77)

Nivolumab+ipilimumab vs nivolumab - HR (95% CI): 0.84 (0.68, 1.04)

Figure 6: Overall survival by PD-L1 expression: 5% cut off (CA209067) - Minimum follow-up of 90 months

PD-L1 expression < 5%

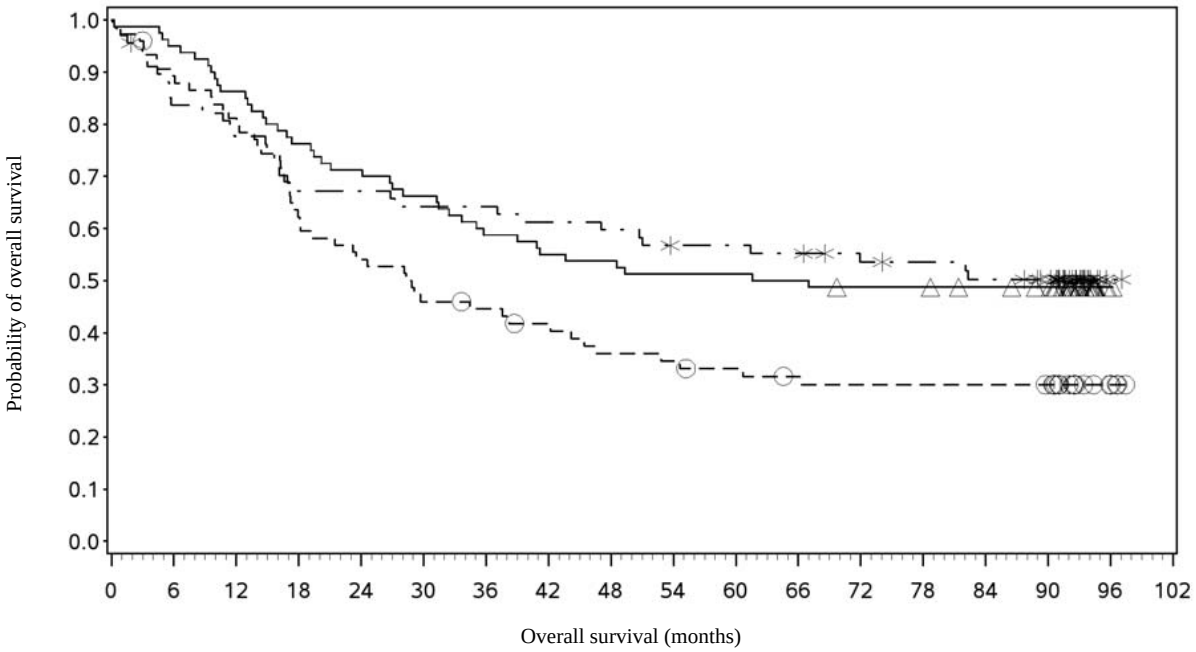


Number of subjects at risk																	
Nivolumab+ipilimumab																	
210	178	146	139	130	123	116	109	106	104	102	100	98	96	96	88	6	-
Nivolumab																	
208	169	144	123	112	108	102	92	90	88	86	84	83	80	79	70	3	-
Ipilimumab																	
202	158	124	99	80	69	59	57	55	50	46	41	39	38	38	33	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 109/210), median and 95% CI: 65.94 (32.72, N.A.)
—△—— Nivolumab (events: 121/208), median and 95% CI: 35.94 months (23.06, 60.91)
- - -❍- - - Ipilimumab (events: 157/202), median and 95% CI: 18.40 months (13.70, 22.51)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.51 (0.40, 0.66)
Nivolumab vs. ipilimumab - HR (95% CI): 0.62 (0.49, 0.79)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.83 (0.64, 1.07)

PD-L1 expression ≥ 5%



Number of subjects at risk

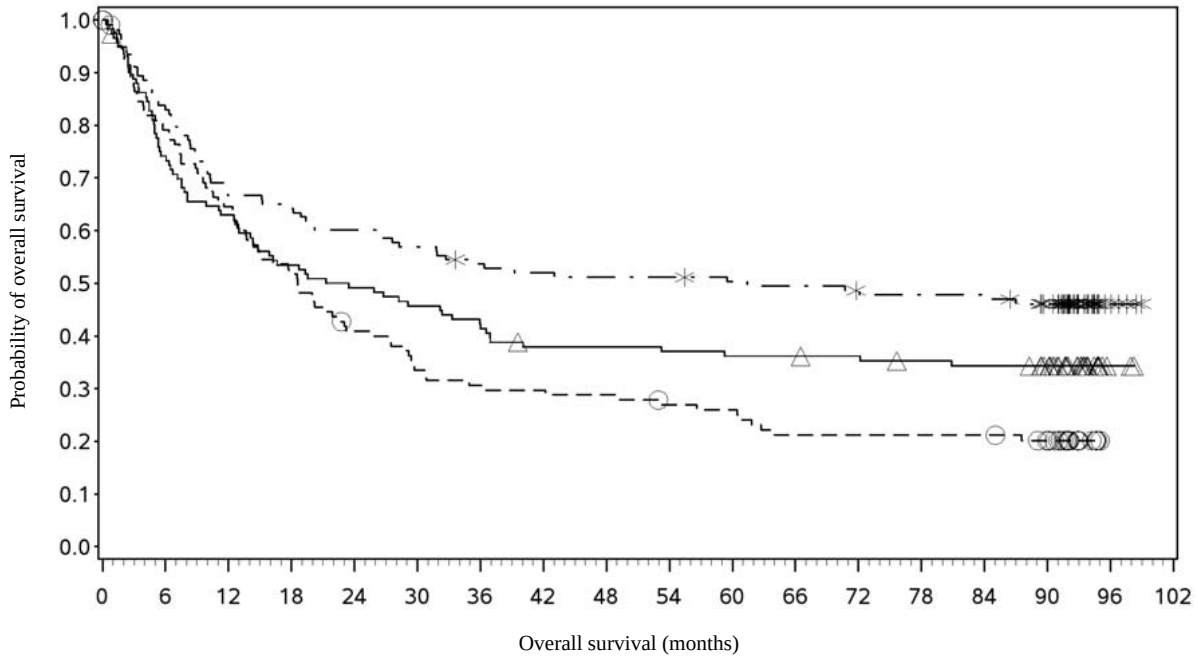
Nivolumab+ipilimumab																	
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1	-
Nivolumab																	
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1	-
Ipilimumab																	
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4	-

- - -✳- - - Nivolumab+ipilimumab (events: 33/68), median and 95% CI: N.A. (39.06, N.A.)
----△---- Nivolumab (events: 41/80), median and 95% CI: 64.28 months (33.64, N.A.)
- - -❍- - - Ipilimumab (events: 51/75), median and 95% CI: 28.88 months (18.10, 44.16)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.61 (0.39, 0.94)
Nivolumab vs. ipilimumab - HR (95% CI): 0.61 (0.41, 0.93)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.99 (0.63, 1.57)

Figure 7: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 90 months

PD-L1 expression < 1%



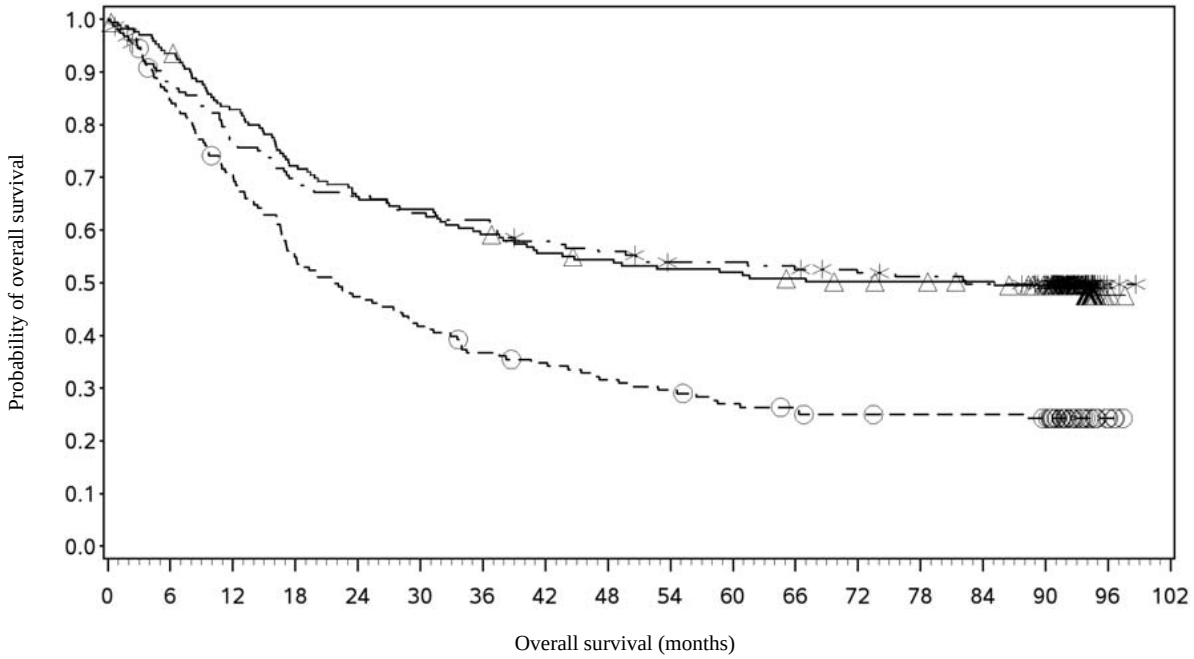
Number of subjects at risk

Nivolumab+ipilimumab																	
123	102	82	79	74	70	65	63	62	62	62	60	59	57	56	50	5	-
Nivolumab																	
117	86	73	62	57	53	49	43	43	42	41	41	40	38	37	33	2	-
Ipilimumab																	
113	87	71	57	44	36	33	32	31	28	27	22	22	22	22	18	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 66/123), median and 95% CI: 61.44 (26.45, N.A.)
——△—— Nivolumab (events: 76/117), median and 95% CI: 23.46 months (13.01, 36.53)
- - -O- - - Ipilimumab (events: 87/113), median and 95% CI: 18.56 months (13.67, 23.20)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.55 (0.40, 0.76)
Nivolumab vs. ipilimumab - HR (95% CI): 0.77 (0.57, 1.05)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.71 (0.51, 0.99)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab+ipilimumab																	
155	132	116	105	101	96	94	87	84	79	79	77	74	72	70	65	2	-
Nivolumab																	
171	159	140	122	112	108	100	93	90	87	86	83	81	80	78	70	2	-
Ipilimumab																	
164	137	113	88	76	67	58	54	49	46	41	39	36	35	35	33	4	-

- - -✳- - - Nivolumab+ipilimumab (events: 76/155), median and 95% CI: 82.30 (39.06, N.A.)
----△---- Nivolumab (events: 86/171), median and 95% CI: 85.09 months (39.00, N.A.)
- - -❍- - - Ipilimumab (events: 121/164), median and 95% CI: 21.49 months (16.85, 29.08)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.70)
Nivolumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.69)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 1.01 (0.74, 1.37)

Minimum follow-up for the analysis of ORR was 90 months. Responses are summarised in Table 14.

Table 14: Objective response (CA209067)

	nivolumab + ipilimumab (n = 314)	**nivolumab (n = 316)**	**ipilimumab (n = 315)**
Objective response	183 (58%)	142 (45%)	60 (19%)
(95% CI)	(52.6, 63.8)	(39.4, 50.6)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.35	3.5	
(95% CI)	(4.38, 9.22)	(2.49, 5.16)	
Complete response (CR)	71(23%)	59 (19%)	19 (6%)
Partial response (PR)	112 (36%)	83 (26%)	41 (13%)
Stable disease (SD)	38 (12%)	29 (9%)	69 (22%)
Duration of response			
Median (range), months	N.A. (69.1-N.A.)	90.8 (45.7-N.A.)	19.3 (8.8-47.4)
Proportion ≥ 12 months in duration	68%	73%	44%
Proportion ≥ 24 months in duration	58%	63%	30%
ORR (95% CI) by tumour PD-L1 expression			
< 5%	56% (48.7, 62.5) n = 210	43% (36, 49.8) n = 208	18% (12.8, 23.8) n = 202
≥ 5%	72% (59.9, 82.3) n = 68	59% (47.2, 69.6) n = 80	21% (12.7, 32.3) n = 75
< 1%	54% (44.4, 62.7) n = 123	36% (27.2, 45.3) n = 117	18% (11.2, 26.0) n = 113
≥ 1%	65% (56.4, 72) n = 155	55% (47.2, 62.6) n = 171	20% (13.7, 26.4) n = 164

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab alone. The observed PFS results at 18 months of follow-up and ORR and OS results at 28 months of follow-up were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level. This observation was maintained with the OS results with a minimum follow-up of 90 months.

Among 131 patients who discontinued the combination due to adverse reaction after 28 months of follow-up, the ORR was 71% (93/131) with 20% (26/131) achieving a complete response and median OS was not reached.

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 14) after 90 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 90 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥ 5% were 78.19 months (range: 18.07-N.A.) in the combination arm,77.21 months (range: 26.25-N.A.) in the nivolumab monotherapy arm and 31.28 months (range: 6.08-N.A.) in the ipilimumab arm. At tumour PD-L1 expression <5%, median durations of response were not reached (range: 61.93-N.A.) in the combination arm, were 90.84 months (range: 50.43-N.A.) in the nivolumab monotherapy arm and 19.25 months (range: 5.32-47.44) in the ipilimumab monotherapy arm.

No clear cut off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS and OS. Results from exploratory multivariate analyses

identified patient and tumour characteristics (ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status, and gender) which might contribute to the survival outcome.

Efficacy by BRAF status:
After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.7 months (95% CI: 7.0, 19.32), while those in the nivolumab monotherapy arm had a median PFS of 5.62 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had a median PFS of 3.09 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively.

After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215).

After 90 months of follow-up, in BRAF [V600] mutation-positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab monotherapy arm. Median OS for BRAF [V600] mutation-positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild-type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.66 (95% CI: 0.44, 0.98) for BRAF[V600] mutation-positive patients and 0.95 (95% CI: 0.74, 1.22) for BRAF wild-type patients.

Randomised phase 2 study of nivolumab in combination with ipilimumab and ipilimumab (CA209069)
Study CA209069 was a randomised, Phase 2, double-blind study comparing the combination of nivolumab and ipilimumab with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma with similar inclusion criteria to study CA209067 and the primary analysis in patients with BRAF wild-type melanoma (77% of patients). Investigator assessed ORR was 61% (95% CI: 48.9, 72.4) in the combination arm (n = 72) versus 11% (95% CI: 3.0, 25.4) for the ipilimumab arm (n = 37). The estimated 2 and 3 year OS rates were 68% (95% CI: 56, 78) and 61% (95% CI: 49, 71), respectively, for the combination (n = 73) and 53% (95% CI: 36, 68) and 44% (95% CI: 28, 60), respectively, for ipilimumab (n = 37).

Adjuvant treatment of melanoma

Randomised phase 3 study of nivolumab vs. placebo (CA20976K)
The safety and efficacy of nivolumab 480 mg monotherapy for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA20976K). The study included patients with an ECOG performance status score of 0 or 1 who had Stage IIB or IIC American Joint Committee on Cancer (AJCC), 8th edition, histologically confirmed melanoma that had been completely surgically resected. Enrolment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node biopsy within 12 weeks prior to randomisation. Patients were enrolled regardless of their tumour PD-L1 status. The study excluded patients with ocular/uveal or mucosal melanoma, active autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery.

A total of 790 patients were randomised (2:1) to receive either nivolumab (n = 526) administered intravenously over 30 minutes at 480 mg every 4 weeks or placebo (n = 264) for up to 1 year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by AJCC 8th edition

T-category (T3b vs. T4a vs. T4b). Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 3 years to 5 years. The primary efficacy outcome measure was recurrence-free survival (RFS). RFS, assessed by the investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first. The secondary outcome measures included OS and distant metastasis-free survival (DMFS).

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 19-92), 61% were men, and 98% were white. Baseline ECOG performance status score was 0 (94%) or 1 (6%). Sixty percent had stage IIB and 40% had stage IIC.

At a primary pre-specified interim analysis (minimum follow-up 7.8 months) a statistically significant improvement in RFS was demonstrated with nivolumab compared to placebo with a HR of 0.42 (95% CI: 0.30, 0.59; $p < 0.0001$). At an updated descriptive RFS analysis (minimum follow-up of 15.6 months), nivolumab continued to demonstrate an RFS improvement with a HR of 0.53 (95% CI: 0.40, 0.71). OS was not mature. Results reported from the analyses with minimum follow-up of 15.6 months are summarised in Table 15 and Figure 8.

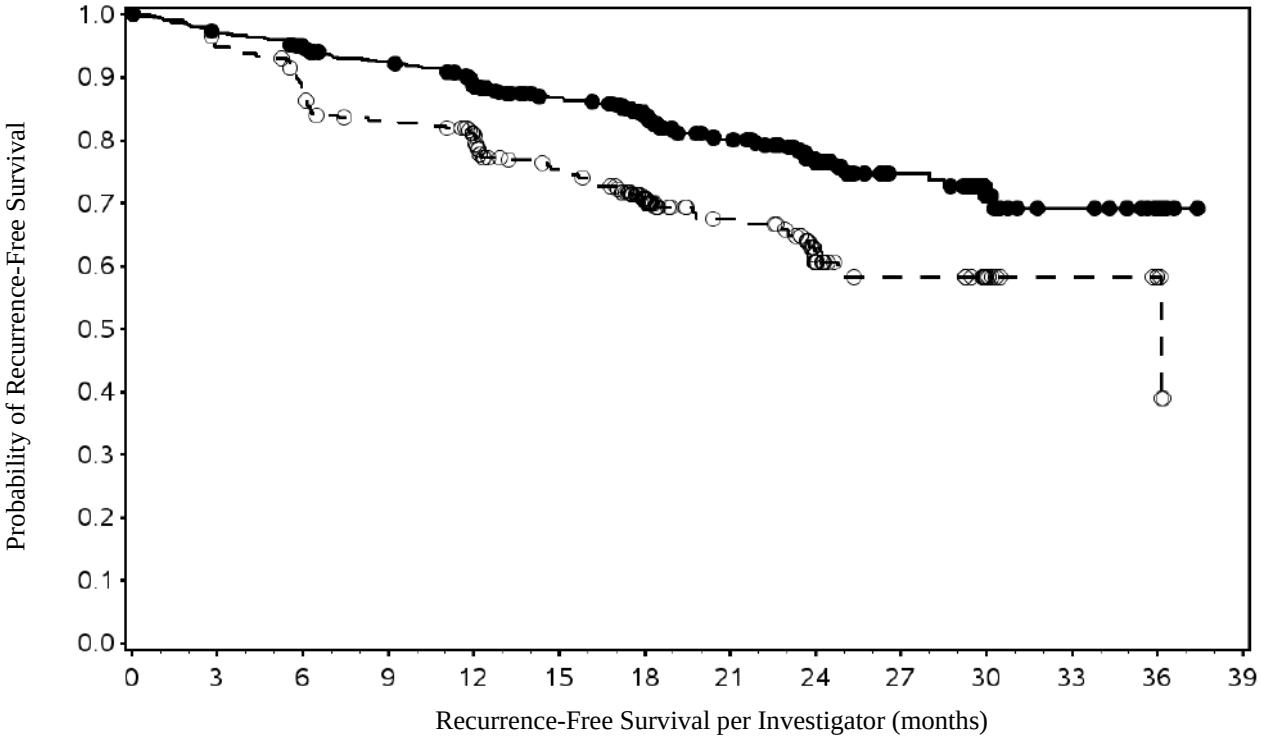
Table 15: Efficacy results (CA20976K)

	nivolumab (n = 526)	**placebo (n = 264)**
Recurrence-free survival with minimum follow-up 15.6 months		
Recurrence-free survival		
Events	102 (19.4%)	84 (31.8%)
Hazard ratio[a]	0.53	
95% CI	(0.40, 0.71)	
Median (95% CI) months	NR	36.14 (24.77, NR)
Rate (95% CI) at 12 months[b]	88.8 (85.6, 91.2)	81.1 (75.7, 85.4)
Rate (95% CI) at 18 months[b]	83.9 (80.3, 86.9)	70.7 (64.5, 76.1)

[a] Based on stratified Cox proportional hazard model.
[b] Based on Kaplan-Meier estimates.

RFS benefit was consistent across key subgroups, including disease stage, T-category, and age.

Figure 8: Recurrence-free survival (CA20976K)



Number of subjects at risk

Nivolumab													
526	492	474	456	422	386	291	210	122	74	40	22	13	0
Placebo													
264	244	224	208	193	165	120	77	44	25	12	7	4	0

—●—— Nivolumab (events 102/526), median and 95% CI: NR
- - -○- - - Placebo (events: 84/264), median and 95% CI: 36.14 (24.77, NR)
Nivolumab vs. Placebo – HR (95% CI): 0.53 (0.40, 0.71)

Based on data cut-off: 21-February-2023, minimum follow-up of 15.6 months

Tumour PD-L1 expression data were available for 302/790 (38.2%) randomised patients (36.3% and 42.0% in the nivolumab and placebo arms, respectively), as PD-L1 expression was not a stratification factor for randomisation. The exploratory RFS analyses by PD-L1 expression showed a HR for nivolumab vs placebo of 0.43 (95% CI: 0.22, 0.84) in patients (N=167) with PD- L1 expression ≥ 1%, 0.82 (95% CI: 0.44, 1.54) in patients (N=135) with PD-L1 expression < 1%, and 0.50 (95% CI: 0.34, 0.73) in patients (N=488) with indeterminate/not reported/not evaluable PD-L1 expression.

Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA209238). The study included adult patients, who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7th edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumour PD-L1 status. Patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomised to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomisation was stratified by tumour PD-L1 expression (≥ 5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumour assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

Baseline characteristics were generally balanced between the two groups. The median age was 55 years (range: 18-86), 58% were men, and 95% were white. Baseline ECOG performance status score was 0 (90%) or 1 (10%). The majority of patients had AJCC Stage III disease (81%), and 19% had Stage IV disease. Forty-eight percent of patients had macroscopic lymph nodes and 32% had tumour ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and 13% BRAF were status unknown. For tumour PD-L1 expression, 34% of patients had PD-L1 expression ≥ 5% and 62% had < 5% as determined by clinical trial assay. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

At a primary pre-specified interim analysis (minimum follow-up 18 months) a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51, 0.83; stratified log-rank p<0.0001) was demonstrated. At an updated descriptive RFS analysis, with minimum follow-up of 24 months RFS improvement was confirmed with HR of 0.66 (95% Cl: 0.54, 0.81; p<0.0001) and OS was not mature. Efficacy results with minimum follow-up of 36 months (RFS pre-specified final analysis) and 48 months (OS pre-specified final analysis) are shown in Table 16 and Figure 9 and 10 (all randomised population).

Table 16: Efficacy results (CA209238)

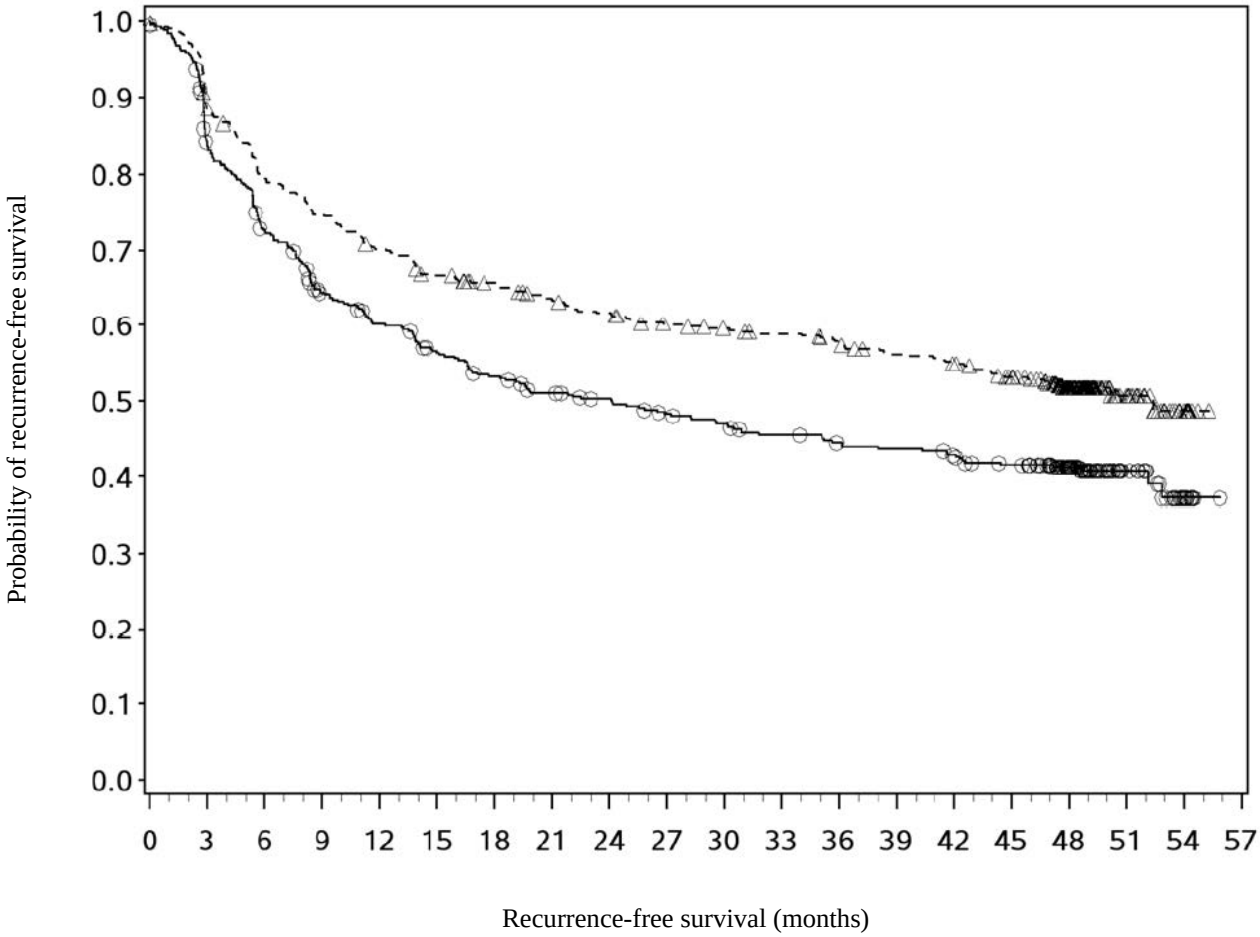
	nivolumab (n = 453)	**ipilimumab 10 mg/kg (n = 453)**
Final pre-specified analysis		
Recurrence-free survival with minimum follow-up 36 months		
Events	188 (41.5%)	239 (52.8%)
Hazard ratio[a]	0.68	
95% CI	(0.56, 0.82)	
p-value	p<0.0001	
Median (95% CI) months	NR (38.67, NR)	24.87 (16.62, 35.12)
Recurrence-free survival with minimum follow-up 48 months		
Events	212 (46.8%)	253 (55.8%)
Hazard ratio[a]	0.71	
95% CI	(0.60, 0.86)	
Median (95% CI) months	52.37 (42.51, NR)	24.08 (16.56, 35.09)
Rate (95% CI) at 12 months	70.4 (65.9, 74.4)	60.0 (55.2, 64.5)
Rate (95% CI) at 18 months	65.8 (61.2, 70.0)	53.0 (48.1, 57.6)
Rate (95% CI) at 24 months	62.6 (57.9, 67.0)	50.2 (45.3, 54.8)
Rate (95% CI) at 36 months	57.6 (52.8, 62.1)	44.4 (39.6, 49.1)
Rate (95% CI) at 48 months	51.7 (46.8, 56.3)	41.2 (36.4, 45.9)

	nivolumab (n = 453)	ipilimumab 10 mg/kg (n = 453)
Final pre-specified analysis Overall survival with minimum follow-up 48 months		
Events	100 (22.1%)	111 (24.5%)
Hazard ratio[a]	0.87	
95.03% CI	(0.66, 1.14)	
p-value	0.3148	
Median (95% CI) months	Not Reached	Not Reached
Rate (95% CI) at 12 months	96.2 (93.9, 97.6)	95.3 (92.8, 96.9)
Rate (95% CI) at 18 months	91.9 (88.9, 94.1)	91.8 (88.8, 94.0)
Rate (95% CI) at 24 months	88.0 (84.6, 90.7)	87.8 (84.4, 90.6)
Rate (95% CI) at 36 months	81.7 (77.8, 85.1)	81.6 (77.6, 85.0)
Rate (95% CI) at 48 months	77.9 (73.7, 81.5)	76.6 (72.2, 80.3)

[a] Derived from a stratified proportional hazards model.

With a minimum follow-up of 36 months, the trial demonstrated a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease. With a minimum follow up of 48 months, shown in Figure 9, the trial continued to demonstrate improvement in RFS in the nivolumab arm compared with the ipilimumab arm. RFS benefit was sustained across all subgroups.

Figure 9: Recurrence-free survival (CA209238)

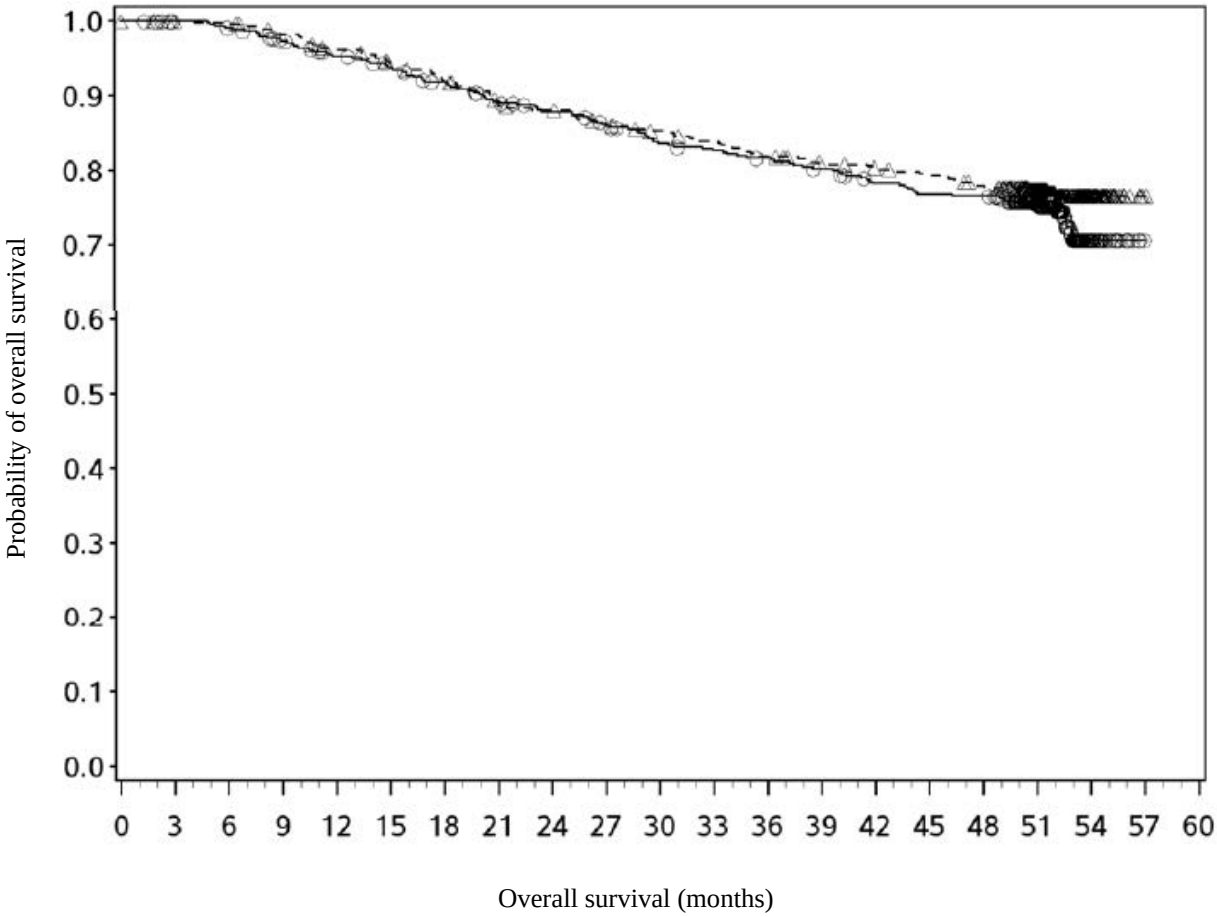


Number of subjects at risk

Nivolumab																				
453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0	
Ipilimumab																				
453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0	

- - -△- - - Nivolumab —○—— Ipilimumab

Figure 10: Overall survival (CA209238)



Number of subjects at risk

Nivolumab																				
453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	237	45	1	0
Ipilimumab																				
453	447	442	430	416	407	395	382	373	363	350	345	340	333	322	316	315	218	40	0	0

- - -△- - - Nivolumab —○—— Ipilimumab

With a minimum follow-up of 48 months, shown in Figure 10, median OS was not reached in either group (HR = 0.87, 95.03% CI: 0.66, 1.14; p-value: 0.3148). The overall survival data are confounded by the effects of effective subsequent anti-cancer therapies. Subsequent systemic therapy was received by 33% and 42% of patients in the nivolumab and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 23% and 34% of patients in the nivolumab and ipilimumab arms, respectively.

Quality of life (QoL) with nivolumab remained stable and close to baseline values during treatment, as assessed by valid and reliable scales like the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EQ-5D utility index and visual analog scale (VAS).

Non-small cell lung cancer

Neoadjuvant treatment of NSCLC

Randomised, open-label, phase 3 study of nivolumab in combination with platinum-based chemotherapy vs. platinum-based chemotherapy (CA209816)

The safety and efficacy of nivolumab in combination with platinum-based chemotherapy for 3 cycles were evaluated in a phase 3, randomised, open-label study (CA209816). The study included patients with ECOG performance status 0 or 1, measurable disease (per RECIST version 1.1), and whose

tumours were resectable, histologically confirmed Stage IB (≥ 4 cm), II, or IIIA NSCLC (per the 7th edition AJCC/Union for International Cancer Control (UICC) staging criteria).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of a patient population with stage II-IIIA disease according to the 7th edition AJCC/UICC staging criteria: any patient with a tumour size ≥5 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations (testing for EGFR mutations or ALK translocations was not mandatory at study entry), Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomisation was stratified by tumour PD-L1 expression level (≥ 1% vs. < 1% or non-quantifiable), disease stage (IB/II vs. IIIA), and gender (male vs. female). Patients were enrolled regardless of their tumour PD-L1 status. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

A total of 358 patients were randomised to receive either nivolumab in combination with platinum-based chemotherapy (n = 179) or platinum-based chemotherapy (n = 179). Patients in the nivolumab in combination with chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for up to 3 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for up to 3 cycles. Platinum-based chemotherapy consisted of investigator's choice of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology). In the chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology).

Tumour assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The primary efficacy outcome measures were event-free survival (EFS) based on BICR assessment and pathological complete response rate (pCR) by blinded-independent pathology review (BIPR). OS was a key secondary efficacy outcome measure and exploratory endpoints included feasibility of surgery.

Baseline characteristics in the ITT population were generally balanced across treatment groups. The median age was 65 years (range: 34-84) with 51% of patients ≥ 65 years and 7% of patients ≥ 75 years; 50% of patients were Asian, 47% were white, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% of patients with PD-L1 ≥ 1% and 43% with PD-L1 < 1%; 5% had Stage IB, 17% had Stage IIA, 13% had Stage IIB, and 64% had Stage IIIA disease; 51% had squamous and 49% had non-squamous histology; and 89% were former/current smokers. Definitive surgery was performed on 83% of the patients in the nivolumab in combination with chemotherapy arm and on 75% of the patients in the chemotherapy arm. Adjuvant systemic treatment was received by 14.8% of patients in the nivolumab in combination with chemotherapy arm and by 25% of patients in the chemotherapy arm.

At the final pCR analysis and pre-specified interim EFS analysis (minimum follow-up 21 months), in all randomised patients, a statistically significant improvement was demonstrated in pCR and EFS for patients randomised to nivolumab in combination with chemotherapy as compared to chemotherapy alone. The pCR response rate was 24% in the nivolumab in combination with chemotherapy arm and 2.2% in the chemotherapy arm (difference of pCR 21.6, 99% CI: 13.0, 30.3; odds ratio of pCR 13.9, 99% CI: 3.49, 55.75; stratified p-value < 0.0001). Median EFS was 31.6 months in the nivolumab in combination with chemotherapy arm and 20.8 months in the chemotherapy arm (HR = 0.63, 97.38% CI: 0.43, 0.91; stratified log-rank p-value 0.0052). The HR for OS was 0.57 (99.67% CI: 0.30, 1.07) for nivolumab in combination with chemotherapy vs. chemotherapy.

Exploratory subgroup analysis by tumour PD-L1 expression and disease stage

The key efficacy results for the subgroup of patients with tumour PD-L1 expression ≥ 1% and disease stage II-IIIA from an exploratory analysis with a minimum follow-up of 32.9 months are summarized in Table 17.

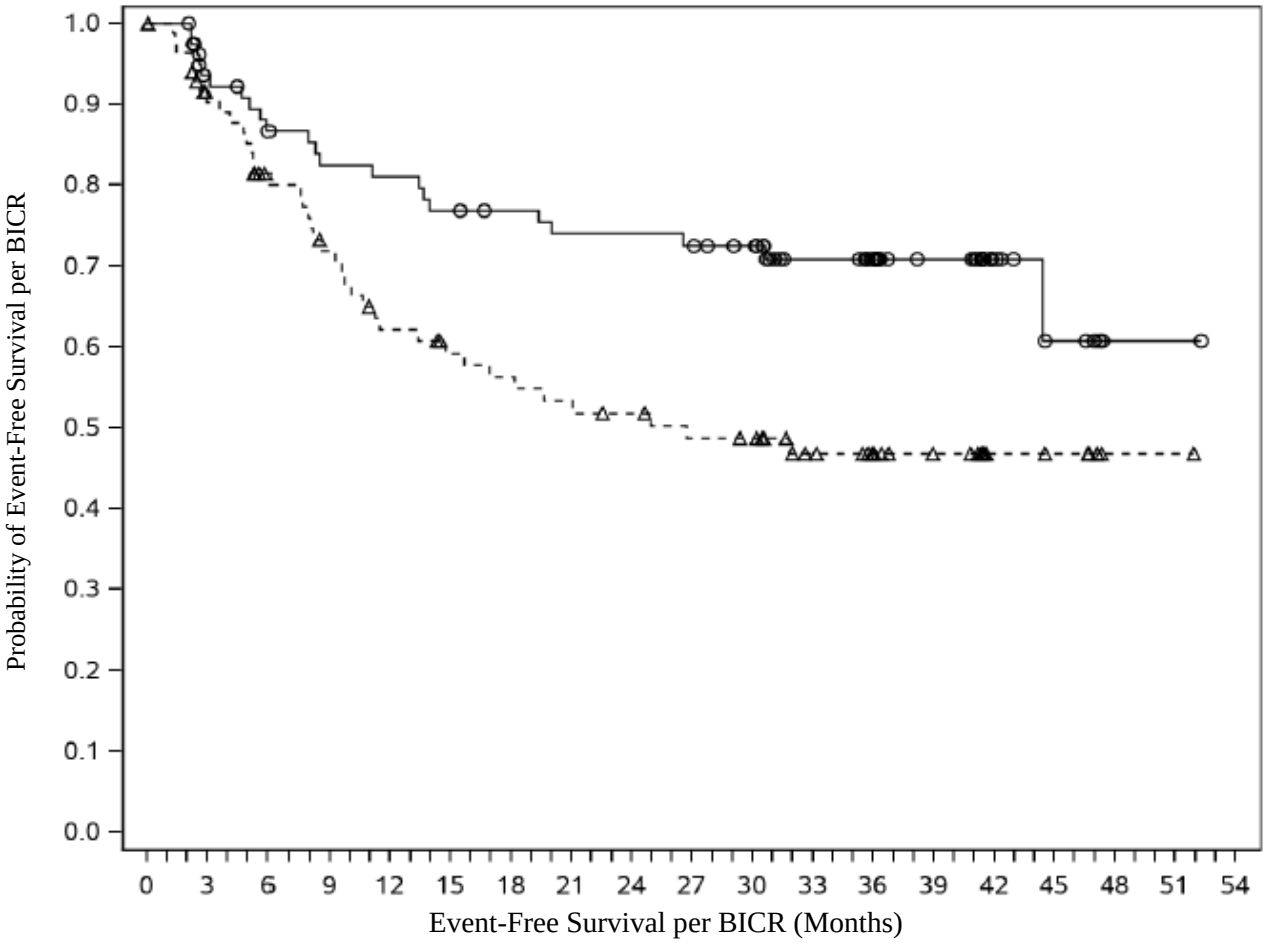
Table 17: Efficacy results in patients with tumour PD-L1 ≥ 1% and stage II-IIIA disease* (CA209816)

	nivolumab + chemotherapy (n = 81)	chemotherapy (n = 86)
Event-free survival per BICR		
Events	22 (27.2%)	39 (45.3%)
Hazard ratio[a] (95% CI)	0.49 (0.29, 0.83)	
Median (months)[b] (95% CI)	NR (44.42, NR)	26.71 (13.40, NR)
Pathologic complete response per BIPR		
Responses	26 (32.1%)	2 (2.3%)
95% CI[c]	(22.2, 43.4)	(0.3, 8.1)
Difference of pCR (95% CI)[d]	29.8% (19.0, 40.7)	

[a] Based on an unstratified Cox proportional hazards model.
[b] Kaplan-Meier estimate.
[c] Based on Clopper and Pearson method.
[d] Two-sided 95% confidence interval for unweighted difference was calculated using Newcombe method.
* 7th edition AJCC/UICC staging criteria.
Minimum follow-up for EFS was 32.9 months, data cut-off: 06-Sep-2022
pCR data cut-off: 28-Jul-2020

The Kaplan-Meier curves for EFS for the subgroup of patients with tumour PD-L1 expression ≥ 1% and stage II-IIIA disease, with a minimum follow-up of 32.9 months, are shown in Figure 11.

Figure 11: Kaplan-Meier curves of EFS in patients with tumour PD-L1 ≥ 1% and stage II-IIIA disease (CA209816)



Number of Subjects at Risk

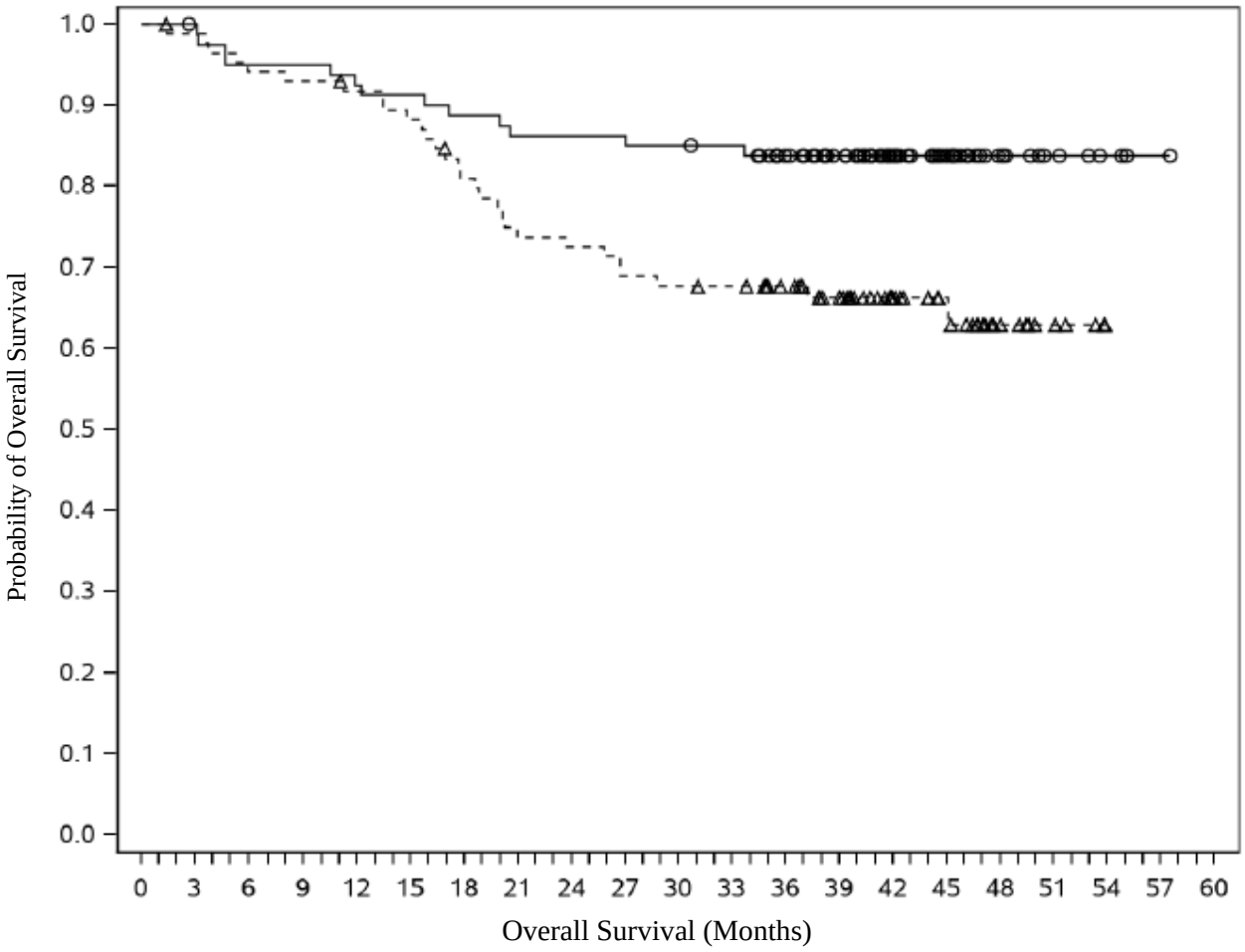
Nivolumab + chemotherapy																		
81	69	62	59	58	55	53	51	51	50	47	37	32	21	10	5	1	1	0
Chemotherapy																		
86	71	60	52	44	40	38	36	34	31	30	23	18	14	7	6	1	1	0

—O—— Nivolumab + chemotherapy (events: 22/81), median and 95% CI: NR (44.42, NR)
- - -△- - - Chemotherapy (events: 39/86), median and 95% CI: 26.71 (13.40, NR)

Based on data cut-off: 06-Sep-2022, minimum follow-up of 32.9 months

At the time of the updated EFS analysis, an interim analysis for OS was performed (minimum follow-up of 32.9 months). The exploratory, descriptive HR for OS in patients with tumour PD-L1 expression ≥ 1% and stage II-IIIA disease was 0.43 (95% CI: 0.22, 0.83) for nivolumab in combination with chemotherapy vs. chemotherapy. The Kaplan-Meier curves for OS for the subgroup of patients with tumour PD-L1 expression ≥ 1% and stage II-IIIA disease, with a minimum follow-up of 32.9 months, are shown in Figure 12.

Figure 12: Kaplan-Meier curves of OS in patients with tumour PD-L1 ≥ 1% and stage II-IIIA disease (CA209816)



Number of Subjects at Risk

Nivolumab + chemotherapy	81	80	76	76	74	73	71	69	69	69	68	67	59	50	33	22	11	6	3	1	0
Chemotherapy	86	84	80	79	77	74	67	61	60	57	56	55	50	41	27	20	10	5	0	0	0

—○—— Nivolumab + chemotherapy (events: 13/81), median and 95% CI: NR
- - -△- - - Chemotherapy (events: 29/86), median and 95% CI: NR

Based on data cut-off: 06-Sep-2022, minimum follow-up of 32.9 months

Neoadjuvant and adjuvant treatment of NSCLC

Randomised, double-blind, phase 3 study of neoadjuvant nivolumab in combination with platinum-based chemotherapy vs. platinum-based chemotherapy and adjuvant nivolumab monotherapy vs. placebo (CA20977T)

The safety and efficacy of nivolumab in combination with platinum-based chemotherapy for 4 cycles, followed by nivolumab monotherapy, were evaluated in a randomised, double-blind study (CA20977T). The study included patients with ECOG performance status 0 or 1 whose tumours were resectable, suspected or histologically confirmed Stage IIA (> 4 cm) to IIIB (T3-T4 N2) NSCLC (per the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual). Patients were enrolled regardless of their tumour PD-L1 status.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of a patient population with stage IIA-IIIB disease according to the 8th edition AJCC/UICC staging criteria: any patient with a tumour size > 4 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic

structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

Patients with unresectable or metastatic NSCLC, EGFR mutations or known ALK translocations (testing for ALK translocations was not mandatory at study entry), brain metastasis, Grade 2 or greater peripheral neuropathy, interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 461 patients were randomised to receive either nivolumab in combination with platinum-based chemotherapy followed by nivolumab monotherapy (n = 229) or platinum-based chemotherapy followed by placebo (n = 232). In the neoadjuvant phase, patients received either nivolumab 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered every 3 weeks, or placebo and platinum-doublet chemotherapy administered every 3 weeks until disease progression or unacceptable toxicity, for up to 4 cycles. Patients in both treatment arms could receive post-operative radiation therapy (PORT) as standard of care. In the adjuvant phase, within 90 days after the surgery patients received either nivolumab 480 mg administered intravenously over 30 minutes every 4 weeks, or placebo administered every 4 weeks for until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles. Platinum-based chemotherapy consisted of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2, and cisplatin 75 mg/m^2 or carboplatin AUC 5 or AUC 6 (non-squamous histology); or cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 (squamous histology).

Stratification factors for randomisation were tumour PD-L1 expression level (≥ 1% versus < 1% versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumour histology (squamous versus nonsquamous). Tumour PD-L1 expression levels were assessed using the PD-L1 IHC 28-8 pharmDx test. Tumour assessments were performed at baseline, within 14 days after the last dose of neoadjuvant treatment and before surgery, within 7 days prior to the start of adjuvant treatment after surgery, every 12 weeks after the first dose of adjuvant treatment for 2 years, then every 24 weeks for up to 5 years until disease recurrence or progression was confirmed by BICR.

Among the 442 patients in CA20977T, 256 (58%) had tumour PD-L1 expression ≥ 1% based on the PD-L1 IHC 28-8 pharmDx test. The median age was 66 years (range: 35 to 86) with 55% of patients ≥ 65 years and 7% of patients ≥ 75 years, 69% were White, 28% were Asian, 2% were Black, and 75% were male. Baseline ECOG performance status was 0 (59%) or 1 (41%); 36% had stage II and 63% had stage III disease; 24% were N1 and 39% were N2; 25% were single-station and 14% were multistation; 61% had tumours with squamous histology and 39% had tumours with non-squamous histology; and 91% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant nivolumab in combination with platinum-doublet chemotherapy followed by adjuvant nivolumab arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm. Approximately 5% of patients in each treatment arm received PORT.

The primary efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included overall survival (OS), pathologic complete response (pCR) and major pathologic response as evaluated by blinded independent pathology review (BIPR).

In a pre-specified interim analysis in all randomised patients with a median follow-up of 25.4 months (range: 15.7-44.2 months), the study demonstrated statistically significant improvement of EFS. Median EFS was not reached (95% CI: 28.94, NE) in the nivolumab in combination with chemotherapy/nivolumab arm and 18.43 months (95% CI: 13.63, 28.06) in the placebo with chemotherapy/placebo arm (HR = 0.58, 97.36% CI: 0.42, 0.81; stratified log-rank p-value 0.00025). In a pre-specified interim analysis in all randomised patients with a median follow-up of 41 months

(range: 31.3-59.8 months), median OS was not reached in both the nivolumab in combination with chemotherapy/nivolumab arm and in the placebo with chemotherapy/placebo arm (HR = 0.85, 97.63% CI: 0.58, 1.25).

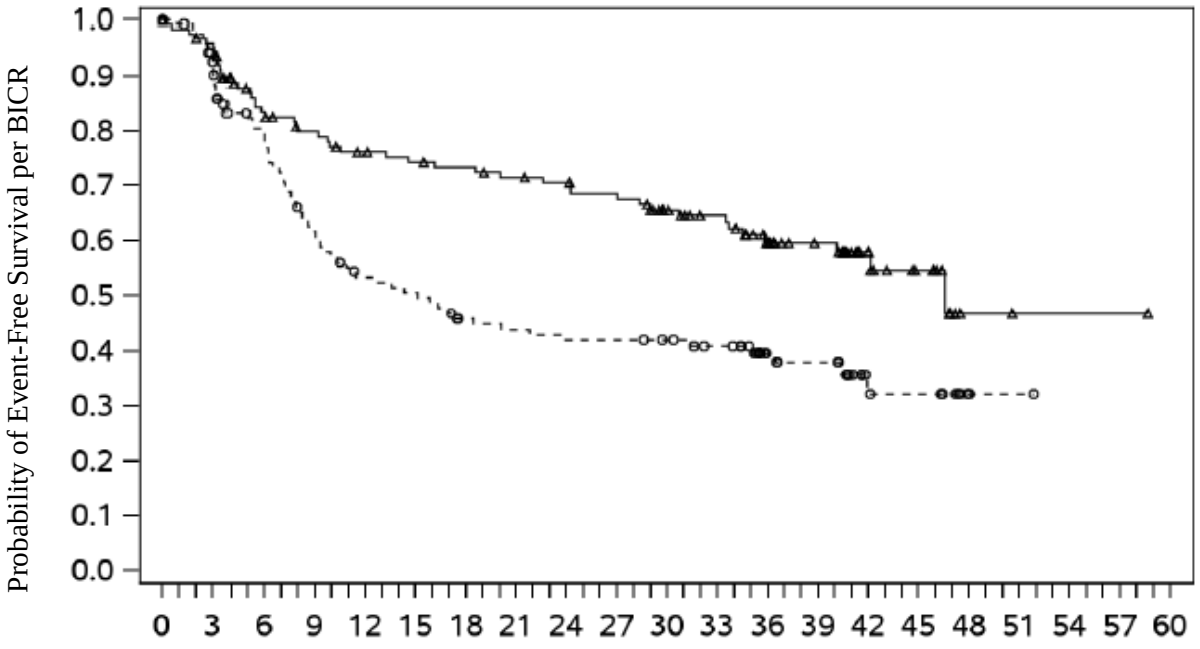
Exploratory subgroup analysis by tumour PD-L1 expression
EFS for the subgroup of patients with tumour PD-L1 expression ≥ 1%, with a median follow-up of 41 months (range: 31.3-59.8 months), are presented in Table 18 and Figure 13.

Table 18: Efficacy results in patients with tumour PD-L1 ≥ 1% (CA20977T)

	nivolumab with chemotherapy/ nivolumab (n = 128)	**placebo with chemotherapy/ placebo (n = 128)**
Event-free survival (EFS) per BICR		
Events (%)	47 (37%)	70 (55%)
Median (months)[a] (95% CI)	46.55 (35.81, NE)	15.08 (9.33, 31.41)
Hazard Ratio[b] (95% CI)	0.53 (0.36, 0.76)	

NE = non-estimable
Minimum follow-up for EFS was 31.3 months; data cut-off: 11-Nov-2024.
[a] Kaplan-Meier estimate.
[b] Based on an unstratified Cox proportional hazard model.

Figure 13: Kaplan-Meier curves of EFS in patients with tumour PD-L1 ≥ 1% (CA20977T)



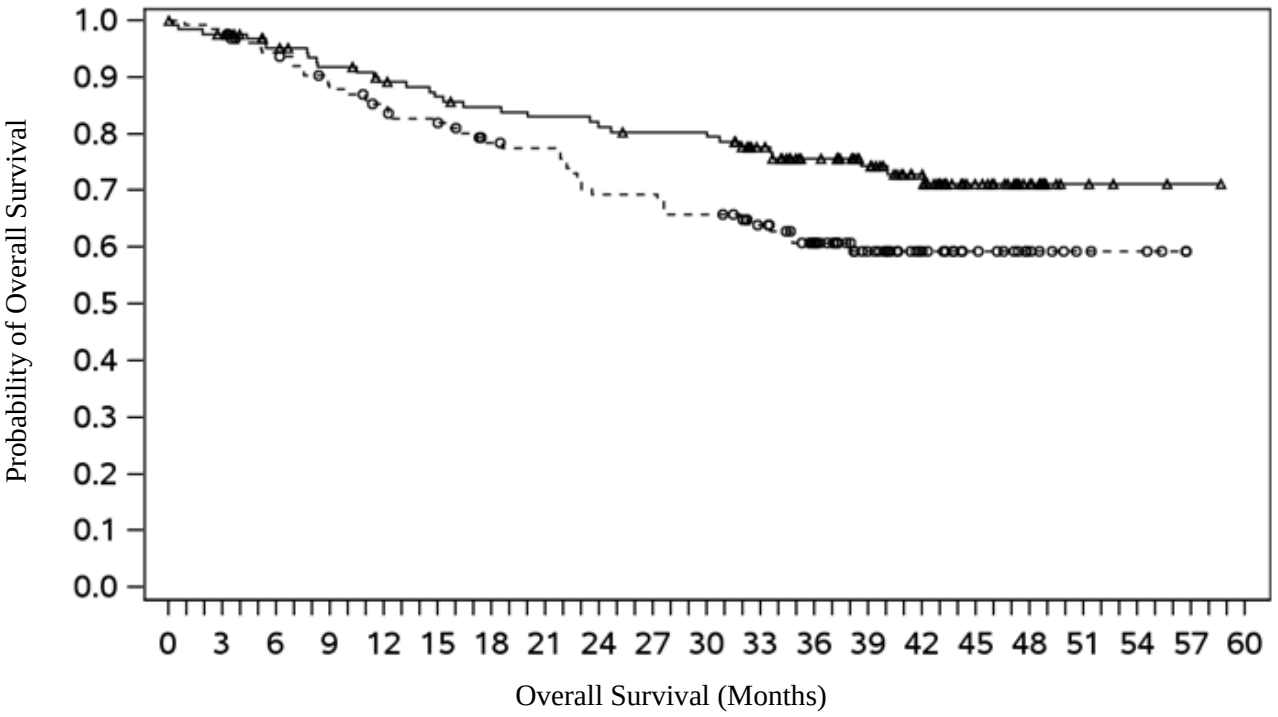
Number of Subjects at Risk

Nivolumab + chemotherapy/Nivolumab																				
128	119	95	89	83	80	78	75	73	70	61	55	44	35	17	11	2	1	1	1	0
Placebo + chemotherapy/Placebo																				
128	110	87	68	57	54	46	44	42	42	40	36	23	20	9	8	2	1	0	0	0

—△—— Nivolumab + chemotherapy/Nivolumab (events: 47/128), median and 95% CI:46.55 (35.81, NE)
- - -❍- - - Placebo + Chemotherapy/Placebo (events: 70/128), median and 95% CI: 15.08 (9.33, 31.41)
Based on data cut-off 11-Nov-2024, minimum follow-up of 31.3 months

At the time of the updated EFS analysis, an interim analysis for OS was performed (minimum follow-up of 31.3 months). The exploratory, descriptive HR for OS in patients with tumour PD-L1 expression ≥ 1% was 0.61 (95% CI: 0.39, 0.97) for the nivolumab in combination with chemotherapy/nivolumab arm vs. the placebo with chemotherapy/placebo arm. The Kaplan-Meier curves for OS for the subgroup of patients with tumour PD-L1 expression ≥ 1% are shown in Figure 14.

Figure 14: Kaplan-Meier curves of OS in patients with tumour PD-L1 ≥ 1% (CA20977T)



Number of Subjects at Risk

Nivolumab + chemotherapy/Nivolumab																			
128	123	114	108	103	99	96	94	92	90	90	80	67	55	42	26	15	4	2	1	0
Placebo + chemotherapy/Placebo																			
128	126	116	106	101	96	88	86	77	77	73	65	54	36	25	17	10	5	4	0	0

—△—— Nivolumab + chemotherapy/Nivolumab (events: 31/128), median and 95% CI: NR
- - -❍- - - Placebo + Chemotherapy/Placebo (events: 46/128), median and 95% CI: NR (38.08, NE)
Based on data cut-off 11-Nov-2024, minimum follow-up of 31.3 months

First-line treatment of NSCLC

Randomised phase 3 study of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)
The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated in a phase 3, randomised, open-label study (CA2099LA). The study included patients (18 years or older) with histologically confirmed non-squamous or squamous Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumour PD-L1 status.

Patients with sensitising EGFR mutations or ALK translocations, active (untreated) brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents. Randomisation was stratified by histology (squamous vs non-squamous), tumour PD-L1 expression level (≥ 1% vs < 1%), and gender (male vs female).

A total of 719 patients were randomised to receive either nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the nivolumab in combination with ipilimumab and platinum-based chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-based chemotherapy administered every 3 weeks for 2 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for 4 cycles; non-squamous patients could receive optional pemetrexed maintenance therapy.

Platinum-based chemotherapy consisted of carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

CA2099LA baseline characteristics were generally balanced across all treatment groups. The median age was 65 years (range: 26-86) with 51% ≥ 65 years of age and 10% ≥ 75 years of age. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% of patients with PD-L1 ≥ 1% and 37% with PD-L1 < 1%, 31% had squamous and 69% had non-squamous histology, 17% had brain metastases, and 86% were former/current smokers. No patients received prior immunotherapy.

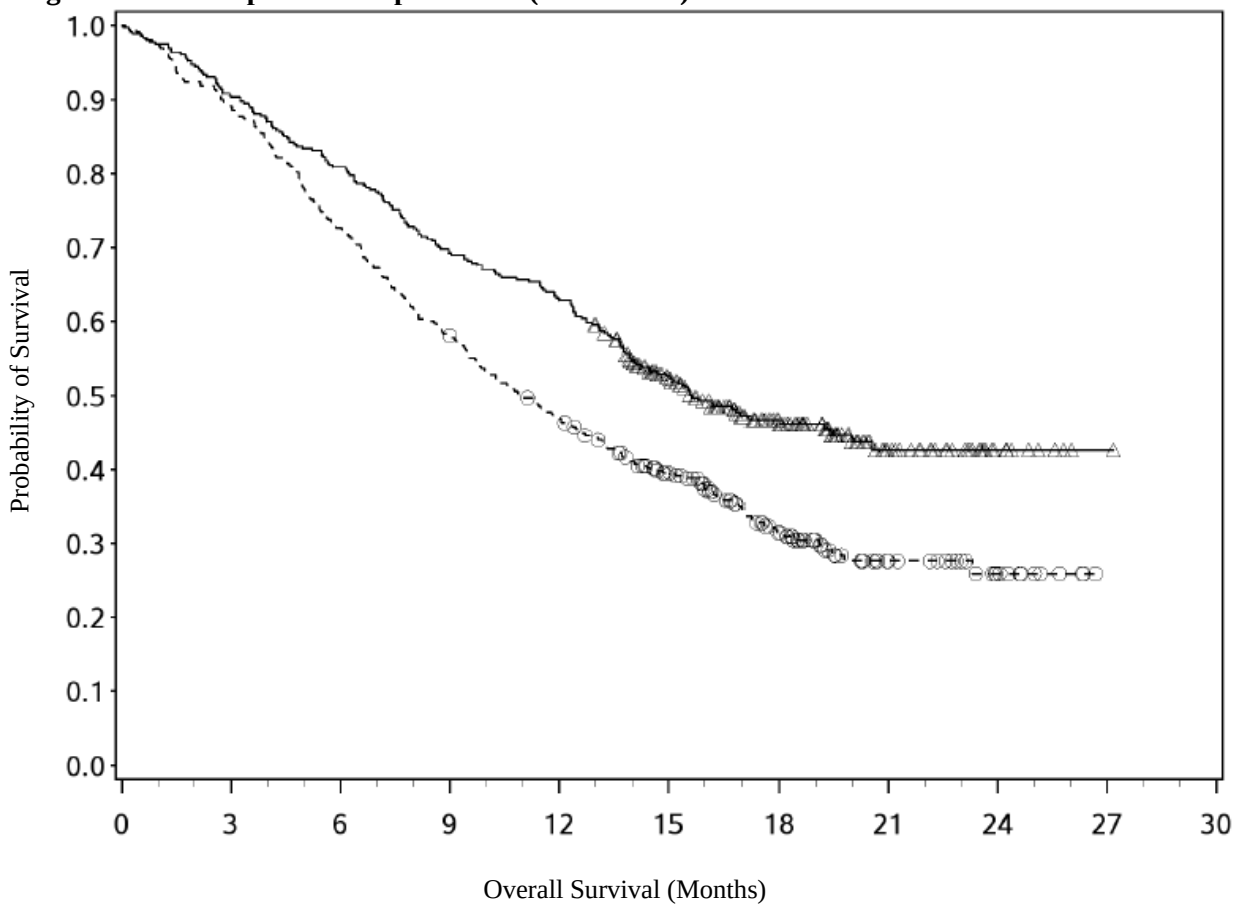
CA2099LA primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR for patients randomised to nivolumab in combination with ipilimumab and platinum-based chemotherapy as compared to platinum-based chemotherapy alone at the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). Minimum follow-up for OS was 8.1 months.

Efficacy results are shown in Figure 15 (updated OS analysis with a minimum follow-up of 12.7 months) and Table 19 (primary analysis with a minimum follow-up of 8.1 months).

An updated efficacy analysis was performed when all patients had a minimum follow-up of 12.7 months (see Figure 15). At the time of this analysis, the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80) and the hazard ratio for PFS was 0.68 (95% CI: 0.57, 0.82).

Figure 15: Kaplan-Meier plot of OS (CA2099LA)



Number of subjects at risk

Nivolumab + ipilimumab + chemotherapy										
361	326	292	250	227	153	86	33	10	1	0
Chemotherapy										
358	319	260	208	166	116	67	26	11	0	0

—△—— Nivolumab + ipilimumab + chemotherapy (events: 190/361), median and 95% CI: 15.64 (13.93, 19.98)

- - -❍- - - Chemotherapy (events: 242/358), median and 95% CI: 10.91 (9.46, 12.55)

Table 19: Efficacy results (CA2099LA)

	nivolumab + ipilimumab + chemotherapy (n = 361)		**chemotherapy (n = 358)**
Overall survival			
Events	156 (43.2%)		195 (54.5%)
Hazard ratio (96.71% CI)[a]		0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]		0.0006	
Median (months) (95% CI)	14.1 (13.24, 16.16)		10.7 (9.46, 12.45)
Rate (95% CI) at 6 months	80.9 (76.4,84.6)		72.3 (67.4,76.7)

	nivolumab + ipilimumab + chemotherapy (n = 361)		chemotherapy (n = 358)
Progression-free survival			
Events	232 (64.3%)		249 (69.6%)
Hazard ratio (97.48% CI)[a]		0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]		0.0001	
Median (months)[d] (95% CI)	6.83 (5.55, 7.66)		4.96 (4.27, 5.55)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)		35.9 (30.5, 41.3)
Overall response rate[e]	136 (37.7%)		90 (25.1%)
(95% CI)	(32.7, 42.9)		(20.7, 30.0)
Stratified CMH test p-value[f]		0.0003	
Complete response (CR)	7 (1.9%)		3 (0.8%)
Partial response (PR)	129 (35.7%)		87 (24.3%)
Duration of response			
Median (months) (95% CI)[d]	10.02 (8.21, 13.01)		5.09 (4.34, 7.00)
% with duration ≥ 6 months[g]	74		41

[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0329 for this interim analysis.
[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.
[d] Kaplan-Meier estimate.
[e] Proportion with complete or partial response; CI based on the Clopper and Pearson Method.
[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.
[g] Based on Kaplan-Meier estimates of duration of response.
CMH = Cochran-Mantel-Haenszel

Subsequent systemic therapy was received by 28.8% and 41.1% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA4) was received by 3.9% and 27.9% of patients in the combination and chemotherapy arms, respectively.

In study CA2099LA, subgroup descriptive analysis relative to chemotherapy, OS benefit was shown in patients treated with nivolumab in combination with ipilimumab and chemotherapy with squamous histology (HR [95% CI] 0.65 [0.46, 0.93], n = 227) and in patients with non-squamous histology (HR [95% CI] 0.72 [0.55, 0.93], n = 492).

Table 20 summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 20: Efficacy results by tumour PD-L1 expression (CA2099LA)

	nivolumab + ipilimumab + chemo-therapy	**chemo-therapy**	**nivolumab + ipilimumab + chemo-therapy**	**chemo-therapy**	**nivolumab + ipilimumab + chemo-therapy**	**chemo-therapy**	**nivolumab + ipilimumab + chemo-therapy**	**chemo-therapy**
	PD-L1 < 1% (n = 264)		**PD-L1 ≥ 1% (n = 406)**		**PD-L1 ≥ 1% to 49% (n = 233)**		**PD-L1 ≥ 50% (n = 173)**	
OS hazard ratio (95% CI)[a]	0.65 (0.46, 0.92)		0.67 (0.51, 0.89)		0.69 (0.48, 0.98)		0.64 (0.41, 1.02)	
PFS hazard ratio (95% CI)[a]	0.77 (0.57, 1.03)		0.67 (0.53, 0.85)		0.71 (0.52, 0.97)		0.59 (0.40, 0.86)	
ORR %	31.1	20.9	41.9	27.6	37.8	24.5	48.7	30.9

[a] Hazard ratio based on unstratified Cox proportional hazards model.

A total of 70 NSCLC patients aged ≥ 75 years were enrolled in study CA2099LA (37 patients in the nivolumab in combination with ipilimumab and chemotherapy arm and 33 patients in the chemotherapy arm). A HR of 1.36 (95% CI: 0.74, 2.52) in OS and a HR of 1.12 (95% CI: 0.64, 1.96) in PFS was observed for nivolumab in combination with ipilimumab and chemotherapy vs. chemotherapy within this study subgroup. ORR was 27.0% in the nivolumab in combination with ipilimumab and chemotherapy arm and 15.2% in the chemotherapy arm. Forty-three percent of patients aged ≥ 75 years discontinued treatment with nivolumab in combination with ipilimumab and chemotherapy. Efficacy and safety data of nivolumab in combination with ipilimumab and chemotherapy are limited in this patient population.

In a subgroup analysis, a reduced survival benefit for nivolumab in combination with ipilimumab and chemotherapy compared to chemotherapy was observed in patients who were never smokers. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Treatment of NSCLC after prior chemotherapy

Squamous NSCLC

Randomised phase 3 study vs. docetaxel (CA209017)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

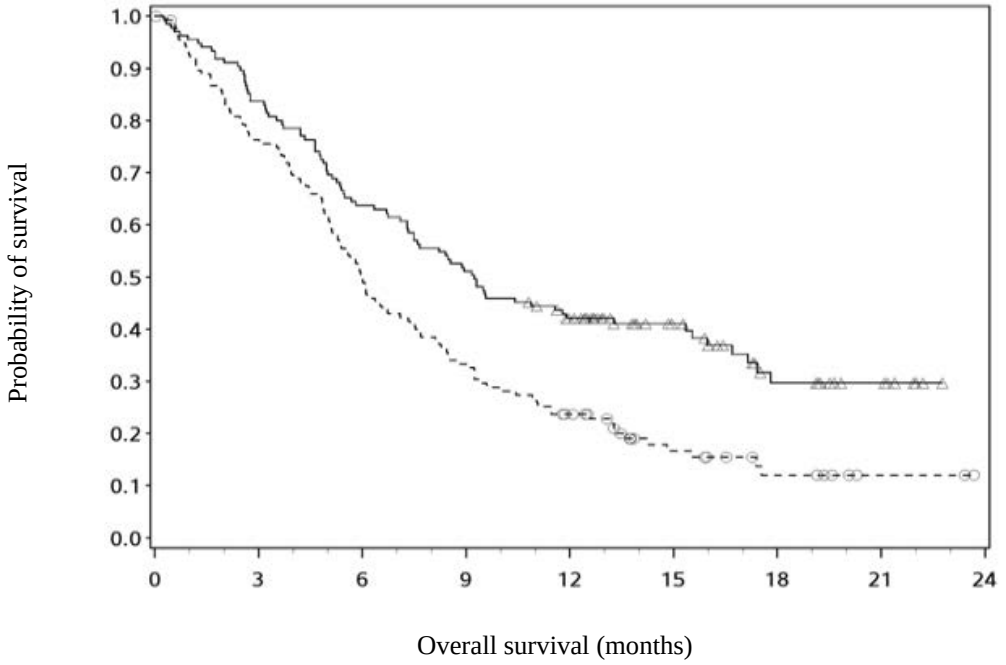
A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the RECIST, version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung cancer symptom score

(LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥ 65 years of age and 11% ≥ 75 years of age. The majority of patients were white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status score was 0 (24%) or 1 (76%).

The Kaplan-Meier curves for OS are shown in Figure 16.

Figure 16: Kaplan-Meier curves of OS (CA209017)



Number of subjects at risk

Nivolumab 3 mg/kg								
135	113	86	69	52	31	15	7	0
Docetaxel								
137	103	68	45	30	14	7	2	0

—△—— Nivolumab 3 mg/kg (events: 86/135), median and 95% CI: 9.23 (7.33, 13.27)
- - -❍- - - Docetaxel (events: 113/137), median and 95% CI: 6.01 (5.13, 7.33)

The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated. With a minimum of 62.6 months follow-up, OS benefit remains consistently demonstrated across subgroups.

Study CA209017 included a limited number of patients ≥ 75 years (11 in the nivolumab group and 18 in the docetaxel group). Nivolumab showed numerically less effect on OS (HR 1.85; 95% CI: 0.76, 4.51), PFS (HR = 1.76; 95%-CI: 0.77, 4.05) and ORR (9.1% vs. 16.7%). Because of the small sample size, no definitive conclusions can be drawn from these data.

Efficacy results are shown in Table 21.

Table 21: Efficacy results (CA209017)

	nivolumab (n = 135)		docetaxel (n = 137)
Primary analysis Minimum follow-up: 10.6 months			
Overall survival			
Events	86 (63.7%)		113 (82.5%)
Hazard ratio		0.59	
96.85% CI		(0.43, 0.81)	
p-value		0.0002	
Median (95% CI) months	9.23 (7.33, 13.27)		6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1 (33.7, 50.3)		23.7 (16.9, 31.1)
Confirmed objective response	27 (20.0%)		12 (8.8%)
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Odds ratio (95% CI)		2.64 (1.27, 5.49)	
p-value		0.0083	
Complete response (CR)	1 (0.7%)		0
Partial response (PR)	26 (19.3%)		12 (8.8%)
Stable disease (SD)	39 (28.9%)		47 (34.3%)
Median duration of response			
Months (range)	Not reached (2.9-20.5^{+})		8.4 (1.4^{+}-15.2^{+})
Median time to response			
Months (range)	2.2 (1.6-11.8)		2.1 (1.8-9.5)
Progression-free survival			
Events	105 (77.8%)		122 (89.1%)
Hazard ratio		0.62	
95% CI		(0.47, 0.81)	
p-value		< 0.0004	
Median (95% CI) (months)	3.48 (2.14, 4.86)		2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)		6.4 (2.9, 11.8)
Updated analysis Minimum follow-up: 24.2 months			
Overall survival[a]			
Events	110 (81.4%)		128 (93.4%)
Hazard ratio		0.62	
95% CI		(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)		8 (4.3, 13.3)
Confirmed objective response	20.0%		8.8%
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Median duration of response			
Months (range)	25.2 (2.9-30.4)		8.4 (1.4^{+}-18.0^{+})

	nivolumab (n = 135)		docetaxel (n = 137)
Progression-free survival			
Rate (95% CI) at 24 months	15.6 (9.7, 22.7)		All patients had either progressed, were censored, or lost to follow-up
	Updated analysis Minimum follow-up: 62.6 months		
Overall survival[a]			
Events	118 (87.4%)		133 (97.1%)
Hazard ratio		0.62	
95% CI		(0.48, 0.79)	
Rate (95% CI) at 60 months	12.3 (7.4, 18.5)		3.6 (1.4, 7.8)
Confirmed objective response	20.0%		8.8%
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Median duration of response			
Months (range)	25.2 (2.9-70.6^{+})		7.5 (0.0^{+}-18.0^{+})
Progression-free survival			
Rate (95% CI) at 60 months	9.4 (4.8, 15.8)		All patients had either progressed, were censored, or lost to follow-up

[a] Six patients (4%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" Denotes a censored observation.

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

Single-arm phase 2 study (CA209063)
Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an ORR of 14.5% (95% CI: 8.7,22.2), a median OS of 8.21 months (95% CI: 6.05,10.9), and a median PFS of 1.87 months (95% CI 1.77,3.15). The PFS was measured by RECIST, version 1.1. The estimated 1-year survival rate was 41%.

Single-arm phase 2 study (CA209171)
Study CA209171 was a single-arm, open label study of nivolumab monotherapy in patients with previously treated advanced or metastatic squamous NSCLC. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 811 treated patients, 103 (13%) had an ECOG performance score of 2, 686 (85%) were < 75 years old and 125 (15%) were ≥ 75 years old. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed ORR are presented in Table 22 below.

Table 22: ORR based on response evaluable patients – total and by subgroup (CA209171)

Results	Total	ECOG PS 2	< 75 years	≥ 75 years
N responders/ N evaluable[a]	66/671	1/64	55/568	11/103
(%)	(9.8)	(6.1)	(9.7)	(10.7)
95% CI[b]	(7.7, 12.3)	(0.0, 8.4)	(7.4, 12.4)	(5.5, 18.3)

[a] includes confirmed and unconfirmed responses, scans were mandatory only at week 8/9 and week 52.
[b] CR+PR, confidence interval based on the Clopper and Pearson method

Non-squamous NSCLC

Randomised phase 3 study vs. docetaxel (CA209057)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

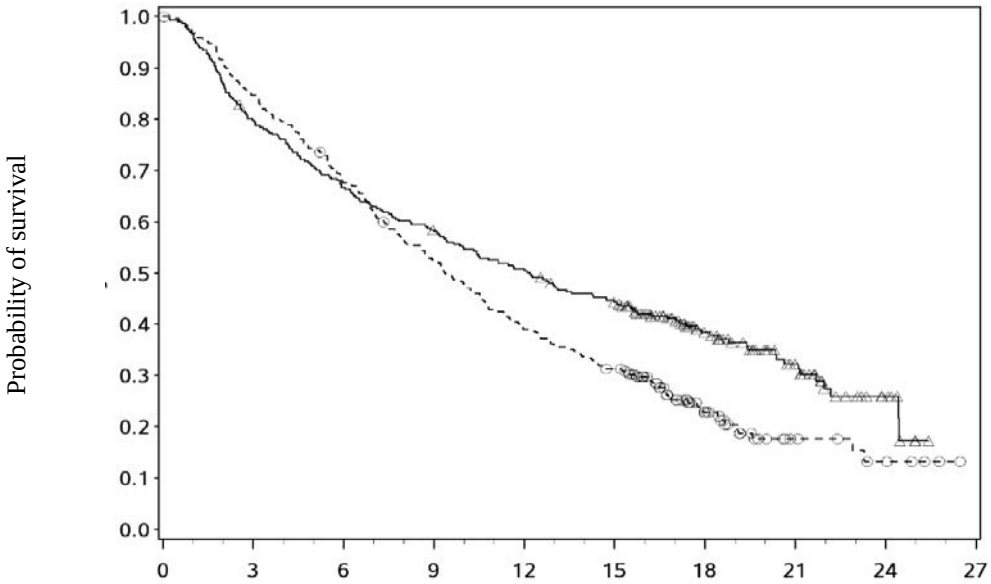
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m^2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted according to the RECIST version 1.1. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy of tumour PD-L1 expression at predefined levels of 1%, 5% and 10%. Assessment according to discrete PD-L1 expression intervals were not included in the prespecified analyses due to the small sample sizes within the intervals.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

The median age was 62 years (range: 21 to 85) with 34% ≥ 65 years of age and 7% ≥ 75 years of age. The majority of patients were white (92%) and male (55%). Baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The Kaplan-Meier curves for OS are shown in Figure 17.

Figure 17: Kaplan-Meier curves of OS (CA209057)



Number of subjects at risk

Nivolumab 3 mg/kg									
292	232	194	169	146	123	62	32	9	0
Docetaxel									
290	244	194	150	111	88	34	10	5	0

—△—— Nivolumab 3 mg/kg (events: 190/292), median and 95% CI: 12.19 (9.66, 14.98)
- - -❍- - - Docetaxel (events: 223/290), median and 95% CI: 9.36 (8.05, 10.68)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 23.

Table 23: Efficacy results (CA209057)

	nivolumab (n = 292)	**docetaxel (n = 290)**
Prespecified interim analysis Minimum follow-up: 13.2 months		
Overall survival		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)

	nivolumab (n = 292)	docetaxel (n = 290)
Confirmed objective response	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response		
Months (range)	17.15 (1.8-22.6+)	5.55 (1.2+-15.2+)
Median time to response		
Months (range)	2.10 (1.2-8.6)	2.61 (1.4-6.3)
Progression-free survival		
Events	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[c]		
Events	228 (78.1%)	247 (85.1%)
Hazard ratio[a]	0.75	
(95% CI)	(0.63, 0.91)	
Rate (95% CI) at 24 months	28.7 (23.6, 34.0)	15.8 (11.9, 20.3)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-33.7+)	5.6 (1.2+-16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9 (8.3, 16.2)	1.0 (0.2, 3.3)

	nivolumab (n = 292)	docetaxel (n = 290)
Updated analysis Minimum follow-up: 62.7 months		
Overall survival[d]		
Events	250 (85.6%)	279 (96.2%)
Hazard ratio[a]	0.70	
(95% CI)	(0.58, 0.83)	
Rate (95% CI) at 60 months	14.0 (10.2, 18.3)	2.1 (0.9, 4.4)
Confirmed objective response	19.5%	12.4%
(95% CI)	(15.1, 24.5)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-70.4+)	5.6 (0.0+-33.4)
Progression-free survival		
Rate (95% CI) at 60 months	7.5 (4.5, 11.4)	All patients had either progressed, were censored, or lost to follow-up

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.
[c] Sixteen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
[d] Seventeen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" Denotes a censored observation.

Quantifiable tumour PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. docetaxel) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (53% vs. 55%), ≥ 5% (41% vs. 38%), or ≥ 10% (37% vs. 35%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to docetaxel, whereas survival was similar to docetaxel in patients with low or no tumour PD-L1 expression. In terms of ORR, increasing PD-L1 expression was associated with larger ORR. Comparable to the overall population, median duration of response was increased with nivolumab vs. docetaxel for patients with no PD-L1 expression (18.3 months vs. 5.6 months) and for patients with PD-L1 expression (16.0 months vs. 5.6 months).

Table 24 summarises results of ORR and OS by tumour PD-L1 expression.

Table 24: ORR and OS by tumour PD-L1 expression (CA209057)

PD-L1 expression	nivolumab	docetaxel	
ORR by tumour PD-L1 expression Minimum follow-up: 13.2 months			
			Odds ratio (95% CI)
< 1%	10/108 (9.3%) 95% CI: 4.5, 16.4	15/101 (14.9%) 95% CI: 8.6, 23.3	0.59 (0.22, 1.48)
≥ 1%	38/123 (30.9%) 95% CI: 22.9, 39.9	15/123 (12.2%) 95% CI: 7.0, 19.3	3.22 (1.60, 6.71)
≥ 1% to < 10%[a]	6/37 (16.2%) 95% CI: 6.2, 32.0	5/44 (11.4%) 95% CI: 3.8, 24.6	1.51 (0.35, 6.85)
≥ 10% to < 50%[a]	5/20 (25.0%) 95% CI: 8.7, 49.1	7/33 (21.2%) 95% CI: 9.0, 38.9	1.24 (0.26, 5.48)
≥ 50%[a]	27/66 (40.9%) 95% CI: 29.0, 53.7	3/46 (6.5%) 95% CI: 1.4, 17.9	9.92 (2.68, 54.09)

PD-L1 expression	nivolumab	docetaxel	
	OS by tumour PD-L1 expression		
	Minimum follow-up: 13.2 months		
	Number of events (number of patients)		**Unstratified hazard ratio (95% CI)**
< 1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥ 1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥ 1% to < 10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥ 10% to < 50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥ 50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)
	Updated analysis		
	Minimum follow-up: 24.2 months		
< 1%	91 (108)	86 (101)	0.91 (0.67, 1.22)
≥ 1%	87 (123)	103 (123)	0.62 (0.47, 0.83)
	Updated analysis		
	Minimum follow-up: 62.7 months		
< 1%	100 (109)	96 (101)	0.87 (0.66, 1.16)
≥1%	96 (122)	119 (123)	0.55 (0.42, 0.73)

[a] Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels.

A higher proportion of patients experienced death within the first 3 months in the nivolumab arm (59/292, 20.2%) as compared to the docetaxel arm (44/290, 15.2%). Results of a post-hoc, exploratory multivariate analysis indicated that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower (e.g., < 50%) or no tumour PD-L1 expression may be at higher risk of death within the first 3 months.

In subgroup analyses, survival benefit compared to docetaxel was not shown for patients who were never-smokers or whose tumours harboured EGFR activating mutations; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Malignant pleural mesothelioma

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy (CA209743)

The safety and efficacy of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks were evaluated in a phase 3, randomised, open-label study (CA209743). The study included patients (18 years or older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first study therapy. Patients were enrolled regardless of their tumour PD-L1 status.

Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the trial. Randomisation was stratified by histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female).

A total of 605 patients were randomised to receive either nivolumab in combination with ipilimumab (n = 303) or chemotherapy (n = 302). Patients in the nivolumab in combination with ipilimumab arm received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks in combination

with ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years. Patients in the chemotherapy arm received chemotherapy for up to 6 cycles (each cycle was 21 days). Chemotherapy consisted of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

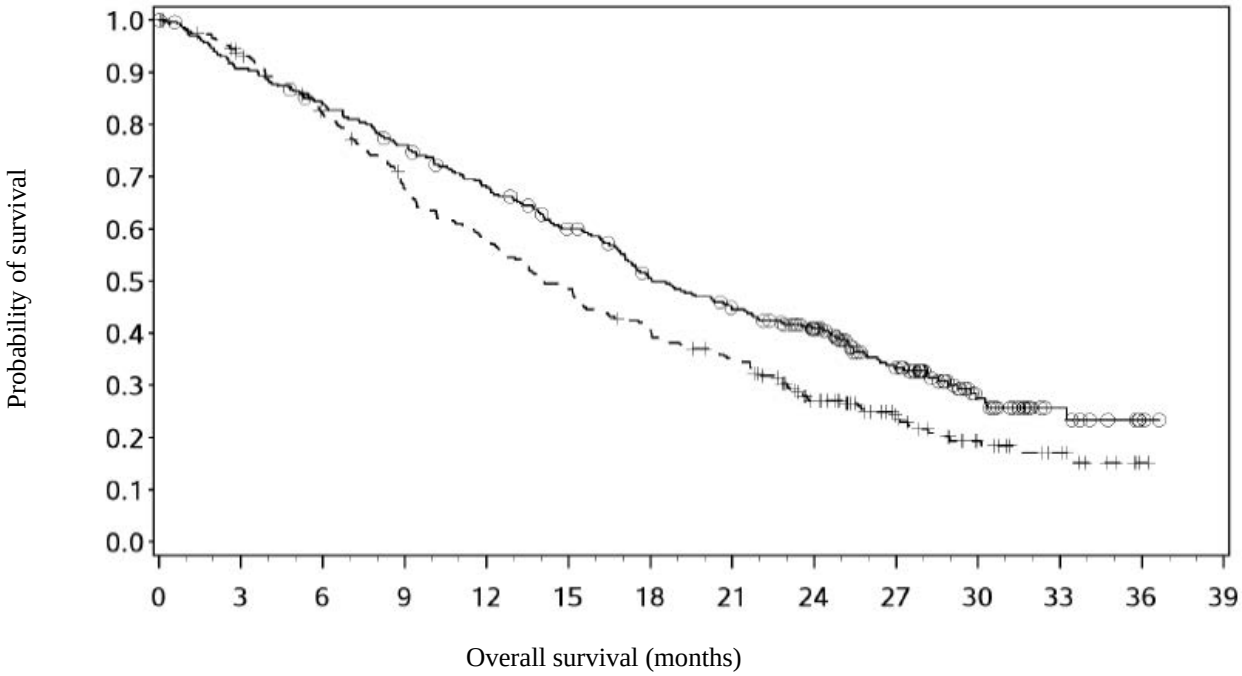
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of age. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 80% of patients with PD-L1 ≥ 1% and 20% with PD-L1 < 1%, 75% had epithelioid and 25% had non-epithelioid histology.

CA209743 primary efficacy outcome measure was OS. Key secondary efficacy endpoints were PFS, ORR, and duration of response as assessed by Blinded Independent Central Review (BICR) utilising modified RECIST criteria for pleural mesothelioma. Descriptive analyses for these secondary endpoints are presented in Table 25.

The study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab in combination with ipilimumab as compared to chemotherapy at the prespecified interim analysis when 419 events were observed (89% of the planned number of events for final analysis). Minimum follow-up for OS was 22 months.

Efficacy results are shown in Figure 18 and Table 25.

Figure 18: Kaplan-Meier curves of OS (CA209743)



Number of subjects at risk

Nivolumab + ipilimumab													
303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemotherapy													
302	268	233	190	162	136	113	95	62	38	20	11	1	0

- - -❍- - - Nivolumab + ipilimumab (events: 200/303), median and 95% CI: 18.07 (16.82, 21.45)
- - -┼- - - Chemotherapy (events: 219/302), median and 95% CI: 14.09 (12.45, 16.23)

Table 25: Efficacy results (CA209743)

	nivolumab + ipilimumab (n = 303)		**chemotherapy (n = 302)**
Overall survival			
Events	200 (66%)		219 (73%)
Hazard ratio (96.6% CI)[a]		0.74 (0.60, 0.91)	
Stratified log-rank p-value[b]		0.002	
Median (months)[c] (95% CI)	18.1 (16.8, 21.5)		14.1 (12.5, 16.2)
Rate (95% CI) at 24 months[c]	41% (35.1, 46.5)		27% (21.9, 32.4)
Progression-free survival			
Events	218 (72%)		209 (69%)
Hazard ratio (95% CI)[a]		1.0 (0.82, 1.21)	
Median (months)[c] (95% CI)	6.8 (5.6, 7.4)		7.2 (6.9, 8.1)

	nivolumab + ipilimumab (n = 303)	chemotherapy (n = 302)
Overall response rate	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response (CR)	1.7%	0
Partial response (PR)	38%	43%
Duration of response		
Median (months)[c]	11.0	6.7
(95% CI)	(8.1, 16.5)	(5.3, 7.1)

[a] Stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.
[c] Kaplan-Meier estimate.

Subsequent systemic therapy was received by 44.2% and 40.7% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA-4) was received by 3.3% and 20.2% of patients in the combination and chemotherapy arms, respectively.

Table 26 summarises efficacy results of OS, PFS, and ORR by histology in prespecified subgroup analyses.

Table 26: Efficacy results by histology (CA209743)

	Epithelioid (n = 471)		Non-epithelioid (n = 134)	
	nivolumab + ipilimumab (n = 236)	chemotherapy (n = 235)	nivolumab + ipilimumab (n = 67)	chemotherapy (n = 67)
Overall survival				
Events	157	164	43	55
Hazard ratio (95% CI)[a]	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Median (months) (95% CI)	18.73 (17.05, 21.72)	16.23 (14.09, 19.15)	16.89 (11.83, 25.20)	8.80 (7.62, 11.76)
Rate (95% CI) at 24 months	41.2 (34.7, 47.6)	31.8 (25.7, 38.1)	39.5 (27.5, 51.2)	9.7 (3.8, 18.9)
Progression-free survival				
Hazard ratio (95% CI)[a]	1.14 (0.92, 1.41)		0.58 (0.38, 0.90)	
Median (months) (95% CI)	6.18 (5.49, 7.03)	7.66 (7.03, 8.31)	8.31 (3.84, 11.01)	5.59 (5.13, 7.16)
Overall response rate (95% CI)[b]	38.6% (32.3, 45.1)	47.2% (40.7, 53.8)	43.3% (31.2, 56.0)	26.9% (16.8, 39.1)
Duration of response Median (months) (95% CI)[c]	8.44 (7.16, 14.59)	6.83 (5.59, 7.13)	24.02 (8.31, N.A.)	4.21 (2.79, 7.03)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Confidence interval based on the Clopper and Pearson method
[c] Median computed using Kaplan-Meier method

Table 27 summarises efficacy results of OS, PFS, and ORR by baseline tumour PD-L1 expression in prespecified subgroup analyses.

Table 27: Efficacy results by tumour PD-L1 expression (CA209743)

	PD-L1 < 1% (n = 135)		PD-L1 ≥ 1% (n = 451)	
	nivolumab + ipilimumab (n = 57)	**chemotherapy (n = 78)**	**nivolumab + ipilimumab (n = 232)**	**chemotherapy (n = 219)**
Overall survival				
Events	40	58	150	157
Hazard ratio (95% CI)[a]	0.94 (0.62, 1.40)		0.69 (0.55, 0.87)	
Median (months) (95% CI)[b]	17.3 (10.1, 24.3)	16.5 (13.4, 20.5)	18.0 (16.8, 21.5)	13.3 (11.6, 15.4)
Rate (95% CI) at 24 months	38.7 (25.9, 51.3)	24.6 (15.5, 35.0)	40.8 (34.3, 47.2)	28.3 (22.1, 34.7)
Progression-free survival				
Hazard ratio (95% CI)[a]	1.79 (1.21, 2.64)		0.81 (0.64, 1.01)	
Median (months) (95% CI)[b]	4.1 (2.7, 5.6)	8.3 (7.0, 11.1)	7.0 (5.8, 8.5)	7.1 (6.2, 7.6)
Overall response rate	21.1%	38.5%	43.5%	44.3%
(95% CI)[c]	(11.4, 33.9)	(27.7, 50.2)	(37.1, 50.2)	(37.6, 51.1)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Median computed using Kaplan-Meier method.
[c] Confidence interval based on the Clopper and Pearson method.

A total of 157 MPM patients aged ≥ 75 years were enrolled in study CA209743 (78 in the nivolumab in combination with ipilimumab arm and 79 in the chemotherapy arm). A HR of 1.02 (95% CI: 0.70, 1.48) in OS was observed for nivolumab in combination with ipilimumab vs. chemotherapy within this study subgroup. A higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older relative to all patients who received nivolumab in combination with ipilimumab was shown (see section 4.8). However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

Renal cell carcinoma

Randomised phase 3 study of nivolumab as monotherapy vs. everolimus (CA209025)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced RCC with a clear cell component was evaluated in a Phase 3, randomised, open-label study (CA209025). The study included patients (18 years or older) who have experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥ 70%. This study included patients regardless of their tumour PD-L1 status. Patients with any history of or concurrent brain metastases, prior treatment with an mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n = 410) administered intravenously over 60 minutes every 2 weeks or everolimus (n = 411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after randomisation and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after

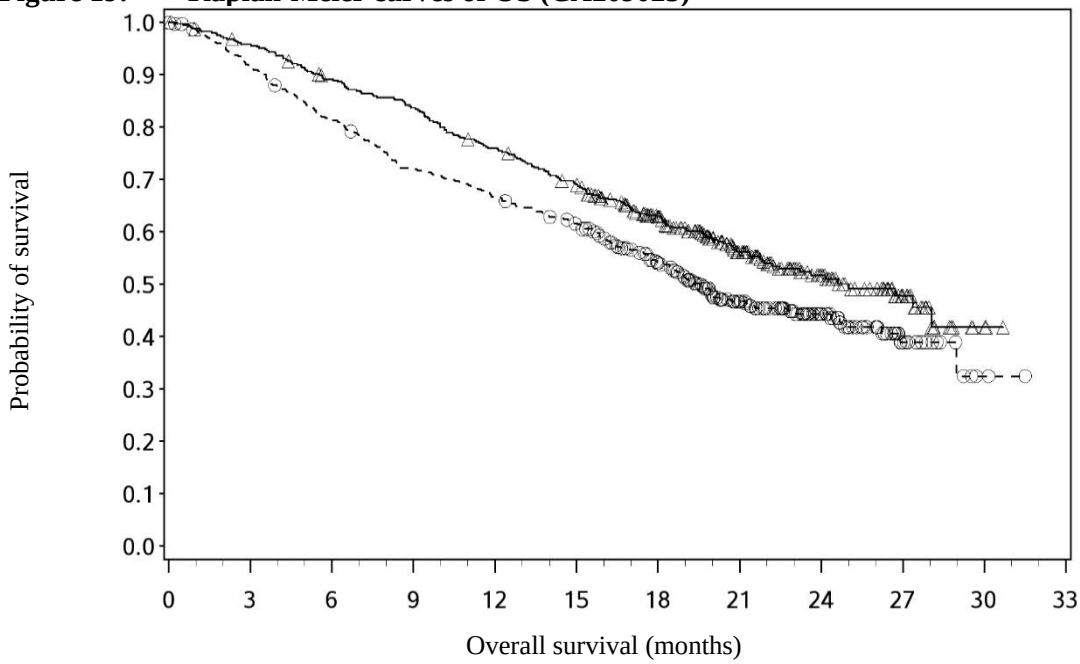
treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥ 65 years of age and 9% ≥ 75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 19.

Figure 19: Kaplan-Meier curves of OS (CA209025)



Number of subjects at risk

Nivolumab											
410	389	359	337	305	275	213	139	73	29	3	0
Everolimus											
411	366	324	287	265	241	187	115	61	20	2	0

—△—— Nivolumab 3 mg/kg (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
- - -❍- - - Everolimus 10 mg (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 28 and Figure 19). OS benefit was observed regardless of tumour PD-L1 expression level.
Efficacy results are shown in Table 28.

Table 28: Efficacy results (CA209025)

	nivolumab (n = 410)		everolimus (n = 411)
Overall survival			
Events	183 (45%)		215 (52%)
Hazard ratio		0.73	
98.52% CI		(0.57, 0.93)	
p-value		0.0018	
Median (95% CI)	25.0 (21.7, NE)		19.6 (17.6, 23.1)
Rate (95% CI)			
At 6 months	89.2 (85.7, 91.8)		81.2 (77.0, 84.7)
At 12 months	76.0 (71.5, 79.9)		66.7 (61.8, 71.0)
Objective response	103 (25.1%)		22 (5.4%)
(95% CI)	(21.0, 29.6)		(3.4, 8.0)
Odds ratio (95% CI)		5.98 (3.68, 9.72)	
p-value		< 0.0001	
Complete response (CR)	4 (1.0%)		2 (0.5%)
Partial response (PR)	99 (24.1%)		20 (4.9%)
Stable disease (SD)	141 (34.4%)		227 (55.2%)
Median duration of response			
Months (range)	11.99 (0.0-27.6^{+})		11.99 (0.0^{+}-22.2^{+})
Median time to response			
Months (range)	3.5 (1.4-24.8)		3.7 (1.5-11.2)
Progression-free survival			
Events	318 (77.6%)		322 (78.3%)
Hazard ratio		0.88	
95% CI		(0.75, 1.03)	
p-value		0.1135	
Median (95% CI)	4.6 (3.71, 5.39)		4.4 (3.71, 5.52)

"+" denotes a censored observation.
NE = non-estimable

The median time to onset of objective response was 3.5 months (range: 1.4-24.8 months) after the start of nivolumab treatment. Forty-nine (47.6%) responders had ongoing responses with a duration ranging from 0.0-27.6^{+} months.

Overall survival could be accompanied by an improvement over time in disease related symptoms and non-disease specific QoL as assessed using valid and reliable scales in the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and the EuroQoL EQ-5D. Apparently meaningful symptom improvement (MID = 2 point change in FKSI-DRS score; $p < 0.001$) and time to improvement (HR = 1.66 (1.33, 2.08), $p < 0.001$) were significantly better for patients on the nivolumab arm. While both arms of the study received active therapy, the QoL data should be interpreted in the context of the open-label study design and therefore cautiously taken.

Phase 3b/4 safety study (CA209374)
Additional safety and descriptive efficacy data are available from study CA209374, an open-label Phase 3b/4 safety study of nivolumab monotherapy (treated with 240 mg every 2 weeks) for the

treatment of patients with advanced or metastatic RCC (n = 142), including 44 patients with non-clear cell histology.

In subjects with non-clear cell histology, at a minimum follow-up of approximately 16.7 months ORR and median duration of response were 13.6% and 10.2 months, respectively. Clinical activity was observed regardless of tumour PD-L1 expression status.

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. sunitinib (CA209214)
The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomisation, Karnofsky performance status <80%, haemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal). This study included patients regardless of their tumour PD-L1 status. Patients with Karnofsky performance status < 70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by IMDC prognostic score and region.

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n = 422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 12 weeks after randomisation and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a BICR in intermediate/poor risk patients.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 21-85) with 38% ≥ 65 years of age and 8% ≥ 75 years of age. The majority of patients were male (73%) and white (87%), and 31% and 69% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The median duration of time from initial diagnosis to randomisation was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day-21.4+ months) in nivolumab with ipilimumab-treated patients and was 7.8 months (range: 1 days-20.2+ months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.

Efficacy results for the intermediate/poor risk patients are shown in Table 29 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 20 (minimum follow-up of 60 months).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis.

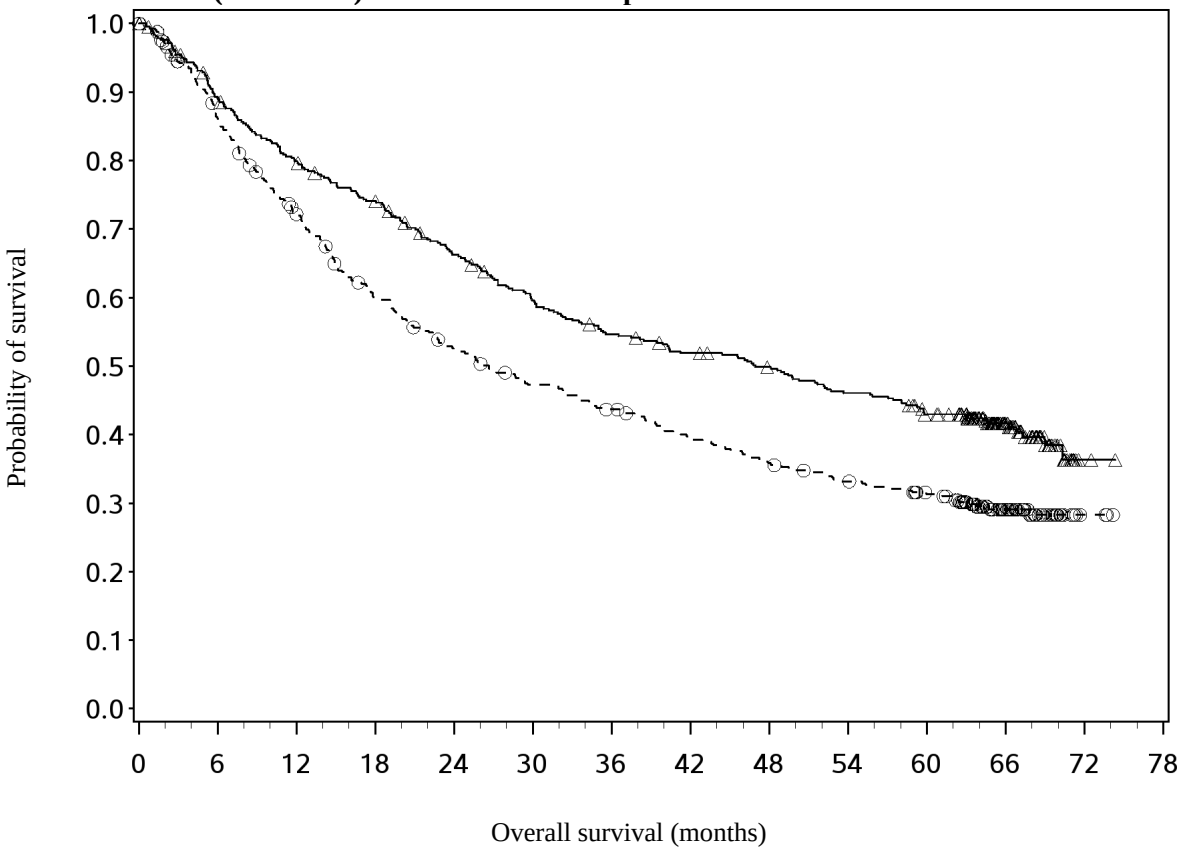
Table 29: Efficacy results in intermediate/poor risk patients (CA209214)

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)
Primary analysis minimum follow-up: 17.5 months			
Overall survival			
Events	140 (33%)		188 (45%)
Hazard ratio[a]		0.63	
99.8% CI		(0.44, 0.89)	
p-value[b, c]		< 0.0001	
Median (95% CI)	NE (28.2, NE)		25.9 (22.1, NE)
Rate (95% CI)			
At 6 months	89.5 (86.1, 92.1)		86.2 (82.4, 89.1)
At 12 months	80.1 (75.9, 83.6)		72.1 (67.4, 76.2)
Progression-free survival			
Events	228 (53.6%)		228 (54.0%)
Hazard ratio[a]		0.82	
99.1% CI		(0.64, 1.05)	
p-value[b,h]		0.0331	
Median (95% CI)	11.6 (8.71, 15.51)		8.4 (7.03, 10.81)
Confirmed objective response (BICR)	177 (41.6%)		112 (26.5%)
(95% CI)	(36.9, 46.5)		(22.4, 31.0)
Difference in ORR (95% CI)[d]		16.0 (9.8, 22.2)	
p-value[e,f]		< 0.0001	
Complete response (CR)	40 (9.4%)		5 (1.2%)
Partial response (PR)	137 (32.2%)		107 (25.4%)
Stable disease (SD)	133 (31.3%)		188 (44.5%)
Median duration of response[g]			
Months (range)	NE (1.4^{+}-25.5^{+})		18.17 (1.3^{+}-23.6^{+})
Median time to response			
Months (range)	2.8 (0.9-11.3)		3.0 (0.6-15.0)
Updated analysis* minimum follow-up: 60 months			
Overall survival			
Events	242 (57%)		282 (67%)
Hazard ratio[a]		0.68	
95% CI		(0.58, 0.81)	
Median (95% CI)	46.95 (35.35, 57.43)		26.64 (22.08, 33.54)
Rate (95% CI)			
At 24 months	66.3 (61.5, 70.6)		52.4 (47.4, 57.1)
At 36 months	54.6 (49.7, 59.3)		43.7 (38.7, 48.5)
At 48 months	49.9 (44.9, 54.6)		35.8 (31.1, 40.5)
At 60 months	43.0 (38.1, 47.7)		31.3 (26.8, 35.9)

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)
Progression-free survival			
Events	245 (57.6%)		253 (60.0%)
Hazard ratio[a]		0.73	
95% CI		(0.61, 0.87)	
Median (95% CI)	11.6 (8.44, 16.63)		8.3 (7.03, 10.41)
Confirmed objective response (BICR)	179 (42.1%)		113 (26.8%)
(95% CI)	(37.4, 47.0)		(22.6, 31.3)
Difference in ORR (95% CI)[d,e]		16.2 (10.0, 22.5)	
Complete response (CR)	48 (11.3%)		9 (2.1%)
Partial response (PR)	131 (30.8%)		104 (24.6%)
Stable disease (SD)	131 (30.8%)		187 (44.3%)
Median duration of response[g]			
Months (range)	NE (50.89-NE)		19.38 (15.38-25.10)
Median time to response			
Months (range)	2.8 (0.9-35.0)		3.1 (0.6-23.6)

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Strata adjusted difference.
[e] Based on the stratified DerSimonian-Laird test.
[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[g] Computed using Kaplan-Meier method.
[h] p-value is compared to alpha 0.009 in order to achieve statistical significance.
"+" denotes a censored observation.
NE = non-estimable
* Descriptive analysis based on data cut-off: 26-Feb-2021.

Figure 20: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214) - Minimum follow-up of 60 months



Number of subjects at risk

Nivolumab + ipilimumab													
425	372	332	306	270	241	220	207	196	181	163	79	2	0
Sunitinib													
422	353	291	237	206	184	169	151	137	125	112	58	3	0

—△—— Nivolumab + ipilimumab (events: 242/425), median and 95.0% CI: 46.95 (35.35, 57.43)
- - -❍- - - Sunitinib (events: 282/422), median and 95.0% CI: 26.64 (22.08, 33.54)

An updated descriptive OS analysis was performed when all patients had a minimum follow-up of 24 months. At the time of this analysis, the hazard ratio was 0.66 (99.8% CI 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression ≥ 1% was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR = 0.52; 95% CI: 0.34, 0.78). For tumour PD-L1 expression < 1%, the median OS was 34.7 months for the nivolumab in combination with ipilimumab, and was 32.2 months in the sunitinib arm (HR = 0.70; 95% CI: 0.54, 0.92).

CA209214 also randomised 249 favourable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. At a minimum of 24 months follow-up, OS in favourable risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710). With 60 months minimum follow-up, the HR for OS was 0.94 (95% CI: 0.65, 1.37).

There are no data on the use of nivolumab in combination with ipilimumab in patients with only a non clear-cell histology in first-line RCC.

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population at a minimum follow-up of 17.5 months. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Randomised phase 3 study of nivolumab in combination with cabozantinib vs. sunitinib (CA2099ER)
The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥ 70%, and measurable disease as per RECIST v1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

A total of 651 patients were randomised to receive either nivolumab 240 mg (n = 323) administered intravenously every 2 weeks in combination with cabozantinib 40 mg once daily orally or sunitinib (n = 328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration for up to 24 months. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. First tumour assessment post-baseline was performed at 12 weeks (± 7 days) following randomisation. Subsequent tumour assessments occurred at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, confirmed by the BICR. The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥ 65 years of age and 9.5% ≥ 75 years of age. The majority of patients were male (73.9%) and white (81.9%). Eight percent of patients were Asian, 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor. For tumour PD-L1 expression, 72.5% of patients had PD-L1 expression < 1% or indeterminate and 24.9% of patients had PD-L1 expression ≥ 1%. 11.5% of patients had tumours with sarcomatoid features. The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in nivolumab with cabozantinib-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 30.

Table 30: Efficacy results (CA2099ER)

	nivolumab + cabozantinib (n = 323)	**sunitinib (n = 328)**
Progression-free survival		
Events	144 (44.6%)	191 (58.2%)
Hazard ratio[a]	0.51	
95% CI	(0.41, 0.64)	
p-value[b, c]	< 0.0001	
Median (95% CI)[d]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)

	nivolumab + cabozantinib (n = 323)	sunitinib (n = 328)
Overall survival		
Events	67 (20.7%)	99 (30.2%)
Hazard ratio[a]	0.60	
98.89% CI	(0.40, 0.89)	
p-value[b,c,e]	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)
Confirmed objective response (BICR)	180 (55.7%)	89 (27.1%)
(95% CI)[f]	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI) [g]	28.6 (21.7, 35.6)	
p-value[h]	< 0.0001	
Complete response (CR)	26 (8.0%)	15 (4.6%)
Partial response (PR)	154 (47.7%)	74 (22.6%)
Stable disease (SD)	104 (32.2%)	138 (42.1%)
Median duration of response[d]		
Months (range)	20.17 (17.31, N.E.)	11.47 (8.31, 18.43)
Median time to response		
Months (range)	2.83 (1.0-19.4)	4.17 (1.7-12.3)

[a] Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.
[b] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥ 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[c] 2-sided p-values from stratified regular log-rank test.
[d] Based on Kaplan-Meier estimates.
[e] Boundary for statistical significance p-value <0.0111.
[f] CI based on the Clopper and Pearson method.
[g] Strata adjusted difference in objective response rate (nivolumab + cabozantinib - sunitinib) based on DerSimonian and Laird.
[h] 2-sided p-value from CMH test.
NE = non-estimable

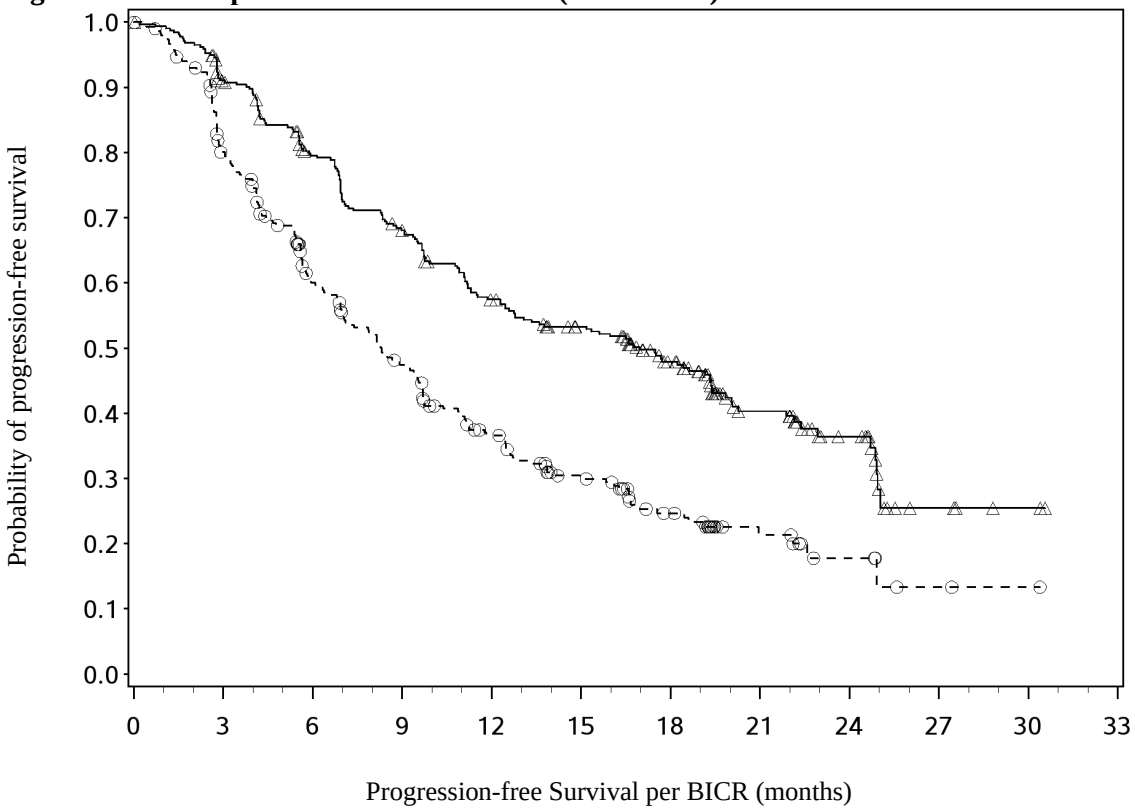
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 30). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. suntinib regardless of the IMDC risk category. Median PFS for the favourable risk group was not reached for nivolumab in combination with cabozantinib, and was 12.81 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.71 months for nivolumab in combination with cabozantinib and was 8.38 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.29 months for nivolumab in combination with cabozantinib and was 4.21 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of tumour PD-L1 expression. Median PFS for tumour PD-L1 expression ≥ 1% was 13.08 months for nivolumab in combination with cabozantinib, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For tumour PD-L1 expression < 1%, the median PFS was 19.84 months for nivolumab in combination with cabozantinib, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16.0 months and a median follow-up of 23.5 months (see Figures 21 and 22). The PFS hazard ratio was 0.52 (95% CI: 0.43, 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50, 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

Figure 21: Kaplan-Meier curves of PFS (CA2099ER)

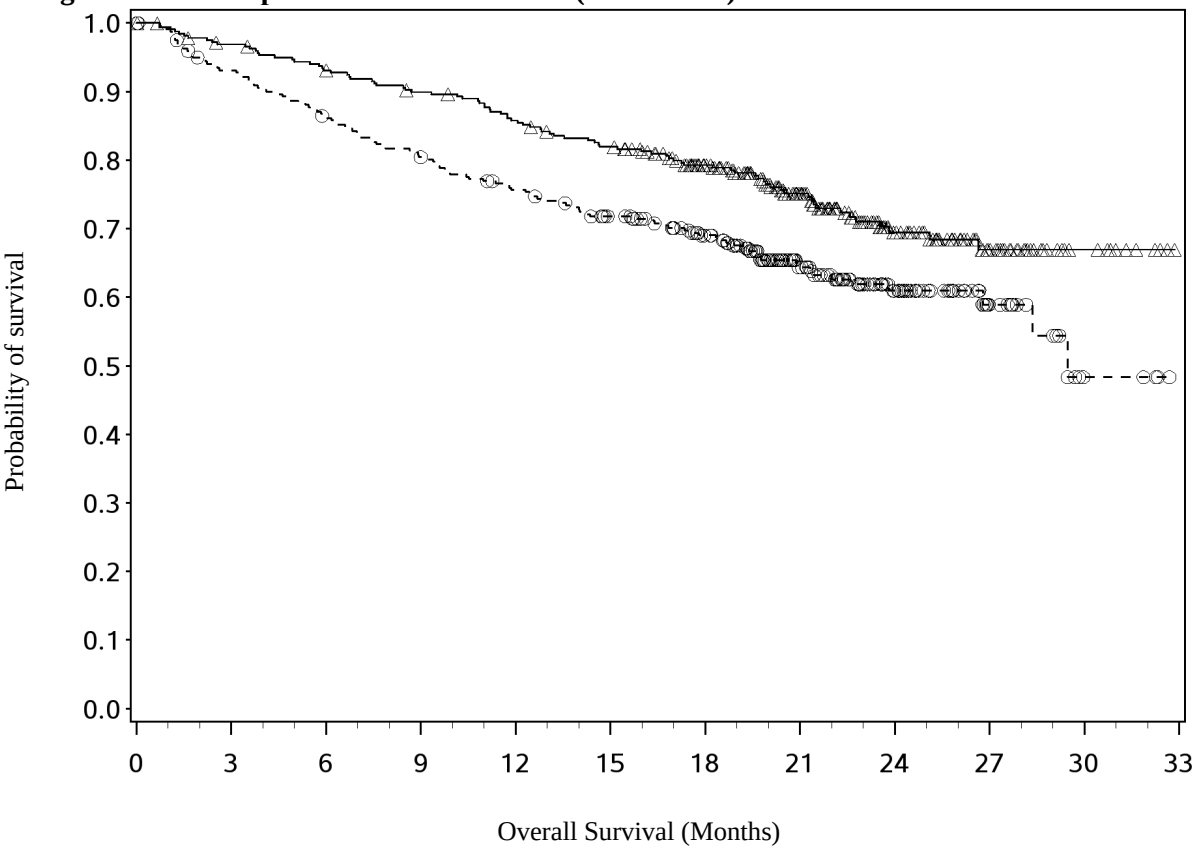


Number of subjects at risk

Nivolumab + cabozantinib											
323	280	236	201	166	145	102	56	26	5	2	0
Sunitinib											
328	230	160	122	87	61	37	17	7	2	1	0

—△—— Nivolumab + cabozantinib (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)
- - -❍- - - Sunitinib (events: 206/328), median and 95.0% CI: 8.31 (6.93, 9.69)

Figure 22: Kaplan-Meier curves of OS (CA2099ER)



Number of subjects at risk

Nivolumab + cabozantinib											
323	308	295	283	269	255	220	147	84	40	10	0
Sunitinib											
328	295	272	254	236	217	189	118	62	22	4	0

—△—— Nivolumab + cabozantinib (events: 86/323), median and 95% CI: NE
- - -❍- - - Sunitinib (events: 116/328), median and 95% CI: 29.47 (28.35, NE)

Classical Hodgkin lymphoma

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of relapsed or refractory cHL following ASCT was evaluated in two multi-centre, open-label, single-arm studies (CA209205 and CA209039).

CA209205 is a Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL. It includes 243 patients who had ASCT; Cohort A included 63 (26%) patients who were brentuximab vedotin naïve; Cohort B included 80 (33%) patients who had received brentuximab vedotin after ASCT failure; and Cohort C included 100 (41%) patients who had received brentuximab vedotin before and/or after ASCT out of which 33 (14%) patients received brentuximab vedotin only prior to ASCT. All patients received nivolumab 3 mg/kg monotherapy intravenously over 60 minutes every 2 weeks. The first tumour assessments were conducted 9 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. The primary efficacy outcome measure was ORR as determined by an IRRC. Additional efficacy measures included duration of response, PFS and OS.

CA209039 is a Phase 1b open-label, multi-centre, dose-escalation, and multidose study of nivolumab in relapsed/refractory hematologic malignancies, including 23 patients with cHL treated with nivolumab 3 mg/kg monotherapy; amongst which, 15 patients received prior brentuximab vedotin treatment as a salvage therapy following ASCT, similar to Cohort B of study CA209205. The first tumour assessments were conducted 4 weeks after the start of treatment and continued thereafter until

disease progression or treatment discontinuation. Efficacy assessments included investigator-assessed ORR, retrospectively evaluated by an IRRC, and duration of response.

Data from the 80 patients from CA209205 Cohort B and from the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Additional data from 100 patients from CA209205 Cohort C who received brentuximab before and/or after ASCT are also presented. Baseline characteristics were similar across the two studies and cohorts (see Table 31 below).

Table 31: Baseline patient characteristics in CA209205 Cohort B, Cohort C and CA209039

	CA209205 Cohort B and CA209039 (n = 95)	CA209205 Cohort B[a] (n = 80)	CA209039 (n = 15)	CA209205 Cohort C[b] (n = 100)
Median age, years (range)	37.0 (18–72)	37.0 (18–72)	40.0 (24–54)	32.0 (19–69)
Gender	61 (64%) M 34 (36%) F	51 (64%) M 29 (36%) F	10 (67%) M 5 (33%) F	56 (56%) M 44 (44%) F
ECOG status				
0	49 (52%)	42 (52.5%)	7 (47%)	50 (50%)
1	46 (48%)	38 (47.5%)	8 (53%)	50 (50%)
≥ 5 prior lines of systemic therapy	49 (52%)	39 (49%)	10 (67%)	30 (30%)
Prior radiation therapy	72 (76%)	59 (74%)	13 (87%)	69 (69%)
Prior ASCT				
1	87 (92%)	74 (92.5%)	13 (87%)	100 (100%)
≥ 2	8 (8%)	6 (7.5%)	2 (13%)	0 (0%)
Years from most recent transplant to first dose of study therapy, median (min-max)	3.5 (0.2–19.0)	3.4 (0.2–19.0)	5.6 (0.5–15.0)	1.7 (0.2–17.0)

[a] 18/80 (22.5%) of the patients in CA209205 Cohort B presented B-Symptoms at baseline.
[b] 25/100 (25%) of the patients in CA209205 Cohort C presented B-Symptoms at baseline.

Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 32.

Table 32: Efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma

Number (n)/ minimum follow-up (months)	CA209205 Cohort B[a] and CA209039 (n = 95/12.0)	CA209205 Cohort B[a] (n = 80/12.0)	CA209039 (n = 15/12.0)
Objective response, n (%); (95% CI)	63 (66%); (56, 76)	54 (68%); (56, 78)	9 (60%); (32, 84)
Complete remission (CR), n (%); (95% CI)	6 (6%); (2, 13)	6 (8%); (3, 16)	0 (0%); (0, 22)
Partial remission (PR), n (%); (95% CI)	57 (60%); (49, 70)	48 (60%); (48, 71)	9 (60%); (32, 84)
Stable disease, n (%)	22 (23)	17 (21)	5 (33)
Duration of response (months)[b]			
Median (95% CI)	13.1 (9.5, NE)	13.1 (8.7, NE)	12.0 (1.8, NE)
Range	0.0^{+}-23.1^{+}	0.0^{+}-14.2^{+}	1.8-23.1^{+}
Median time to response			
Months (range)	2.0 (0.7-11.1)	2.1 (1.6-11.1)	0.8 (0.7-4.1)
Median duration of follow-up			
Months (range)	15.8 (1.9-27.6)	15.4 (1.9-18.5)	21.9 (11.2-27.6)
Progression-free survival			
Rate (95% CI) at 12 months	57 (45, 68)	55 (41, 66)	69 (37, 88)

"+" denotes a censored observation.
[a] Follow-up was ongoing at the time of data submission.
[b] Data unstable due to the limited duration of response for Cohort B resulting from censoring.
NE = non-estimable

Updated efficacy results from longer follow-up data of Cohort B (minimum 68.7 months) and Cohort C (minimum 61.9 months) from CA209205 are presented below in Table 33.

Table 33: Updated efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma from longer follow-up of study CA209205

Number (n)/ minimum follow-up (months)	CA209205 Cohort B (n = 80/68.7)	CA209205 Cohort C (n = 100/61.9)[a]
Objective response, n (%); (95% CI)	57 (71%); (60, 81)	75 (75%); (65, 83)
Complete remission (CR), n (%); (95% CI)	11 (14%); (7, 23)	21 (21%); (14, 30)
Partial remission (PR), n (%); (95% CI)	46 (58%); (46, 69)	54 (54%); (44, 64)
Stable disease, n (%)	14 (18%)	12 (12%)
Duration of response in all responders (months)[b]		
Median (95% CI)	16.6 (9.3, 25.7)	18.2 (11.6, 30.9)
Range	0.0^{+}-71.0^{+}	0.0^{+}-59.8^{+}
Duration of response in CR (months)		
Median (95% CI)	30.3 (2.4, NE)	26.4 (7.1, NE)
Range	0.7^{+}-50.0^{+}	0.0^{+}-55.7^{+}
Duration of response in PR (months)		
Median (95% CI)	10.6 (7.5, 25.3)	14.7 (9.4, 30.4)
Range	0.0^{+}-67.9^{+}	0.0^{+}-55.9^{+}
Median time to response		
Months (range)	2.2 (1.6-11.1)	2.1 (0.8, 17.9)
Median duration of follow-up		
Months (range)	58.5 (1.9-74.3)	53.5 (1.4-70.4)
Progression-free survival		
Median (95% CI)	14.8 (11.0, 19.8)	15.1 (11.1, 19.1)
Rate (95% CI) at 12 months	52 (39, 63)	53 (42, 64)
Rate (95% CI) at 24 months	36 (24, 48)	37 (25, 48)
Rate (95% CI) at 60 months	16 (6, 29)	15 (6, 28)
Overall survival		
Median	Not reached	Not reached
Rate (95% CI) at 12 months	95 (87, 98)	90 (82, 94)
Rate (95% CI) at 24 months	87 (77, 93)	86 (77, 91)
Rate (95% CI) at 60 months	72 (60, 81)	67 (56, 75)

"+" denotes a censored observation.

[a] Patients in Cohort C (n = 33) who have received brentuximab vedotin only prior to ASCT had ORR of 73% (95% CI: 55, 87), CR of 21% (95% CI: 9, 39), PR of 52% (95% CI: 34, 69). Median duration of response was 13.5 months (95% CI: 9.4, 30.9).

[b] Determined for subjects with CR or PR.

NE = non-estimable

B-symptoms were present in 22% (53/243) of the patients in CA209205 at baseline. Nivolumab treatment resulted in rapid resolution of B-symptoms in 88.7% (47/53) of the patients, with a median time to resolution of 1.9 months.

In a post-hoc analysis of the 80 patients in CA209205 Cohort B, 37 had no response to prior brentuximab vedotin treatment. Among these 37 patients, treatment with nivolumab resulted in an ORR of 62.2% (23/37). The median duration of response is 25.6 months (10.6, 56.5) for the 23 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

Squamous cell cancer of the head and neck

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older), with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, recurrent, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or active brain or leptomeningeal metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

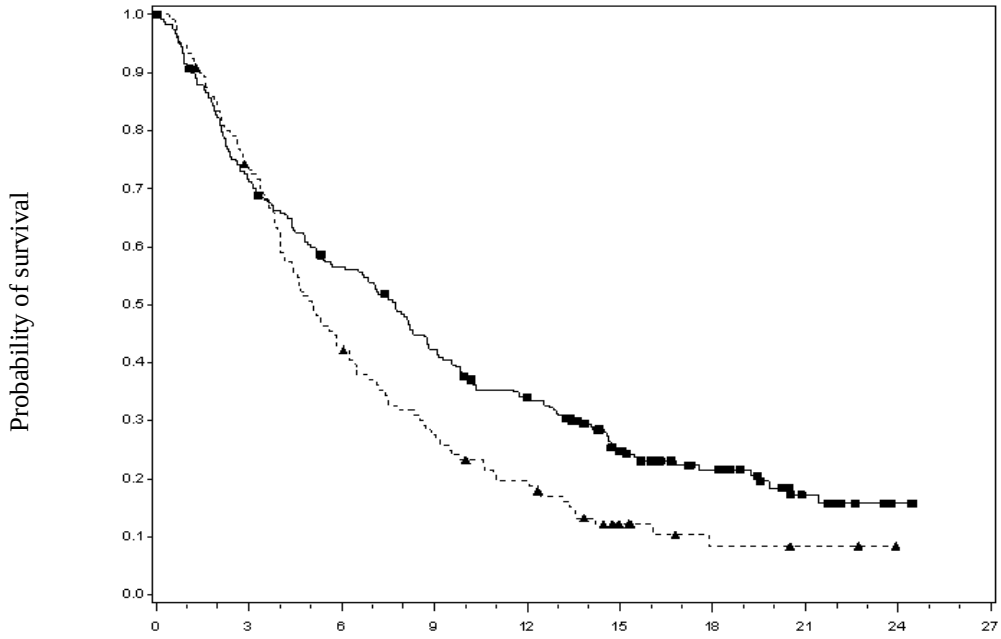
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly, or docetaxel (n = 54) 30 to 40 mg/m^2 weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted in patients receiving nivolumab, if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 60 years (range: 28-83) with 31% ≥ 65 years of age and 5% ≥ 75 years of age, 83% were male, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 77% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 34% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 23. Efficacy results are shown in Table 34.

Figure 23: Kaplan-Meier curves of OS (CA209141)



Overall survival (months)

Number of subjects at risk

Nivolumab								
240	169	132	98	76	45	27	12	3
Investigator's choice								
121	88	51	32	22	9	4	3	0

—■— Nivolumab 3 mg/kg (events: 184/240), median and 95% CI: 7.72 (5.68, 8.77)
- - -▲- - - Investigator's choice (events: 105/121), median and 95% CI: 5.06 (4.04, 6.24)

Table 34: Efficacy results (CA209141)

	nivolumab (n = 240)	**investigator's choice (n = 121)**
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
Progression-free survival		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.97, 3.12)
Rate (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9, 18.3)
Rate (95% CI) at 12 months	9.5 (6.0, 13.9)	2.5 (0.5, 7.8)

	nivolumab (n = 240)	investigator's choice (n = 121)
Confirmed objective response[c]	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)
Median time to response		
Months (range)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
Median duration of response		
Months (range)	9.7 (2.8-20.3+)	4.0 (1.5+-8.5+)

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.
[c] In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

Quantifiable tumour PD-L1 expression was measured in 67% of patients in the nivolumab group and 82% of patients in the investigator's choice group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. investigator's choice) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (55% vs. 62%), ≥ 5% (34% vs. 43%), or ≥ 10% (27% vs. 34%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (see Table 35).

Table 35: OS by tumour PD-L1 expression (CA209141)

PD-L1 Expression	nivolumab	investigator's choice	
	OS by tumour PD-L1 expression		
	Number of events (number of patients)		Unstratified hazard ratio (95% CI)
< 1%	56 (73)	32 (38)	0.83 (0.54, 1.29)
≥ 1%	66 (88)	55 (61)	0.53 (0.37, 0.77)
≥ 5%	39 (54)	40 (43)	0.51 (0.32, 0.80)
≥ 10%	30 (43)	31 (34)	0.57 (0.34, 0.95)

In an exploratory post-hoc analysis using a non-validated assay, both tumour cell PD-L1 expression and tumour-associated immune cell (TAIC) PD-L1 expression were analysed in relation to the magnitude of treatment effect of nivolumab compared to investigator's choice. This analysis showed that not only tumour cell PD-L1 expression but also TAIC PD-L1 expression appeared to be associated with benefit from nivolumab relative to investigator's choice (see Table 36). Due to the small numbers of patients in the subgroups, and exploratory nature of the analysis, no definitive conclusions can be drawn from these data.

Table 36: Efficacy by tumour cell and TAIC PD-L1 expression (CA209141)

	Median OS[a] (months) HR[b] (95% CI)		Median PFS[a] (months) HR[b] (95% CI)		ORR (%) (95% CI)[c]	
	nivolumab	investigator's choice	nivolumab	investigator's choice	nivolumab	investigator's choice
PD-L1 ≥ 1%, PD-L1+ TAIC abundant[d] (61 nivolumab, 47 investigator's choice)	9.10	4.60	3.19	1.97	19.7	0
	0.43 (0.28, 0.67)		0.48 (0.31, 0.75)		(10.6, 31.8)	(0, 7.5)
PD-L1 ≥ 1%, PD-L1+ TAIC rare[d] (27 nivolumab, 14 investigator's choice)	6.67	4.93	1.99	2.04	11.1	7.1
	0.89 (0.44, 1.80)		0.93 (0.46, 1.88)		(2.4, 29.2)	(0.2, 33.9)
PD-L1 < 1%, PD-L1+ TAIC abundant[d] (43 nivolumab, 25 investigator's choice)	11.73	6.51	2.10	2.73	18.6	12.0
	0.67 (0.38, 1.18)		0.96 (0.55, 1.67)		(8.4, 33.4)	(2.5, 31.2)
PD-L1 < 1%, PD-L1+ TAIC rare[d] (27 nivolumab, 10 investigator's choice)	3.71	4.85	1.84	2.12	3.7	10.0
	1.09 (0.50, 2.36)		1.91 (0.84, 4.36)		(< 0.1, 19.0)	(0.3, 44.5)

[a] OS and PFS were estimated using Kaplan-Meier method.
[b] Hazard ratio in each subgroup derived from a Cox proportional hazards model with treatment as the only covariate.
[c] Confidence interval for ORR calculated using the Clopper-Pearson method.
[d] PD-L1+ TAIC in the tumour microenvironment were qualitatively assessed, and characterised as "numerous", "intermediate", and "rare" based on pathologist assessments. "Numerous" and "intermediate" groups were combined to define the "abundant" group.

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV (determined by p16 immunohistochemistry [IHC]). OS benefit was observed regardless of HPV status (HPV-positive: HR = 0.63; 95% CI: 0.38, 1.04, HPV-negative: HR = 0.64; 95% CI: 0.40, 1.03, and HPV-unknown: HR = 0.78; 95% CI: 0.55, 1.10).

Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, and 3-level EQ-5D. Over 15 weeks of follow-up, patients treated with nivolumab exhibited stable PROs, while those assigned to investigator's choice therapy exhibited significant declines in functioning (e.g., physical, role, social) and health status as well as increased symptomatology (e.g., fatigue, dyspnoea, appetite loss, pain, sensory problems, social contact problems). The PRO data should be interpreted in the context of the open-label study design and therefore taken cautiously.

Advanced urothelial carcinoma

Randomised open-label phase 3 study of nivolumab in combination with chemotherapy vs. chemotherapy (CA209901)

The safety and efficacy of nivolumab in combination with cisplatin and gemcitabine followed by nivolumab monotherapy were evaluated in a randomised open-label study CA209901 in cisplatin-eligible patients with unresectable or metastatic urothelial carcinoma. The study included subjects (18 years or older) with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra, who were eligible for cisplatin and gemcitabine. Minor histologic variants (< 50% overall) were acceptable (TCC must have been the dominant histology). All subjects were required to have

measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. No prior systemic anti-cancer therapy for metastatic or surgically unresectable urothelial carcinoma was permitted. Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place ≥ 12 months from completion of therapy. Prior intravesical therapy was permitted if completed at least 4 weeks prior to initiation of study treatment. Radiation therapy (with or without chemotherapy) with curative intent was permitted if treatment was completed ≥ 12 months before enrolment. Palliative radiotherapy was permitted as long as it was completed at least 2 weeks prior to therapy.

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n = 304) or cisplatin and gemcitabine (n = 304). Randomisation was stratified by tumour PD-L1 status (≥ 1% vs. < 1% or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥ 75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed at 1000 mg/m^2 IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m^2 IV over 30 to 120-minutes on Day 1 of the 3 week treatment cycle. A total of 92 patients (49 in the nivolumab in combination with cisplatin and gemcitabine arm and 43 in the cisplatin and gemcitabine arm) switched from cisplatin to carboplatin after at least one cycle of cisplatin.

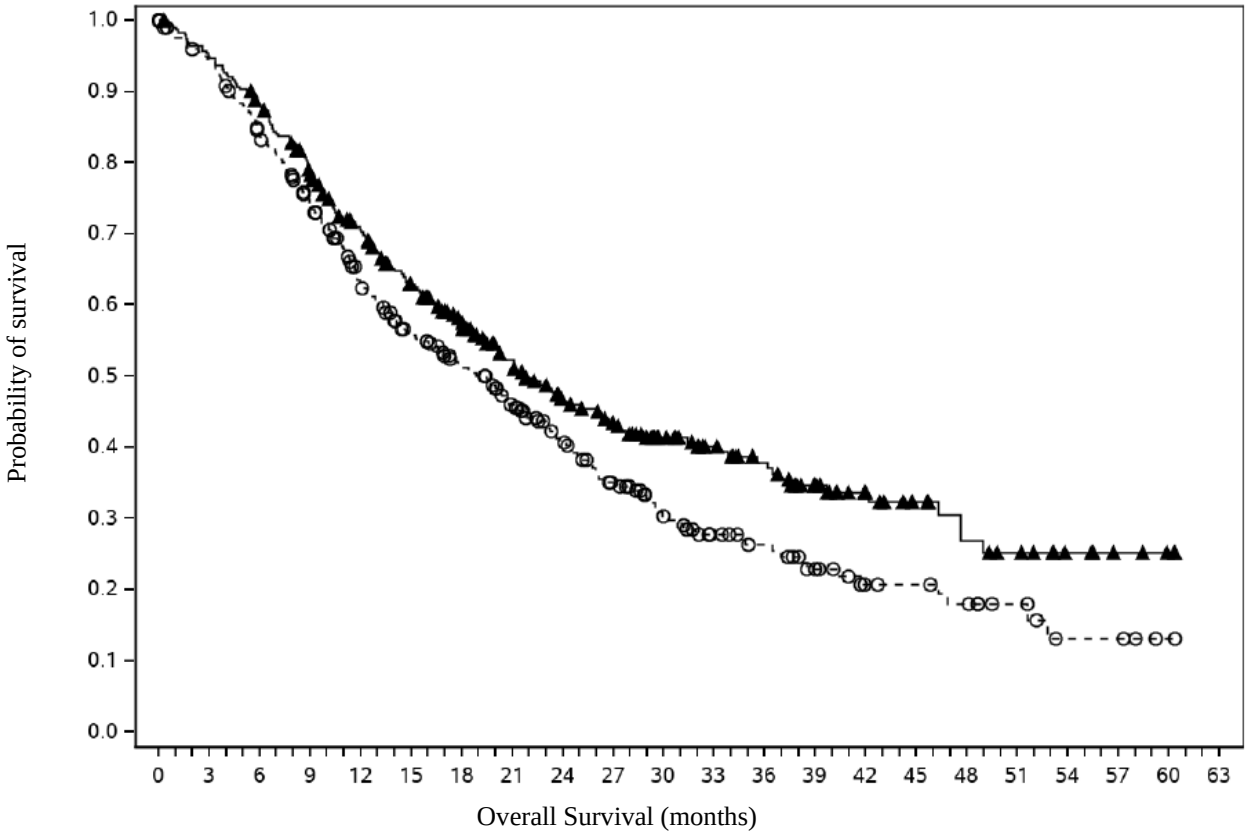
The study demonstrated a statistically significant benefit in OS and PFS for patients randomised to nivolumab in combination with cisplatin and gemcitabine compared to cisplatin and gemcitabine alone. Efficacy results are presented in Table 37 and Figures 24 and 25.

Table 37: Efficacy Results (CA209901)

	nivolumab and cisplatin-gemcitabine chemotherapy (n = 304)	**cisplatin- gemcitabine chemotherapy (n = 304)**
Overall Survival[a]		
Events	172 (56.6)	193 (63.5)
Median (months) (95% CI)	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival[a]		
Events	211 (69.4)	191 (62.8)
Median (months) (95% CI)	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)
Hazard ratio (95% CI)[b]	0.72 (0.59, 0.88)	
p-value[c]	0.0012	
Objective Response Rate		
Responders	175 (57.6)	131 (43.1)
(95% CI)	(51.8, 63.2)	(37.5, 48.9)

[a] Based on Kaplan-Meier Estimates
[b] Stratified Cox proportional hazard model.
[c] 2 sided p-value from stratified log-rank test.

Figure 24: Kaplan Meier curves of OS (CA209901)



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy

304 286 264 228 196 167 142 119 97 84 69 58 48 36 25 20 15 12 7 4 2 0

Gemcitabine-cisplatin chemotherapy

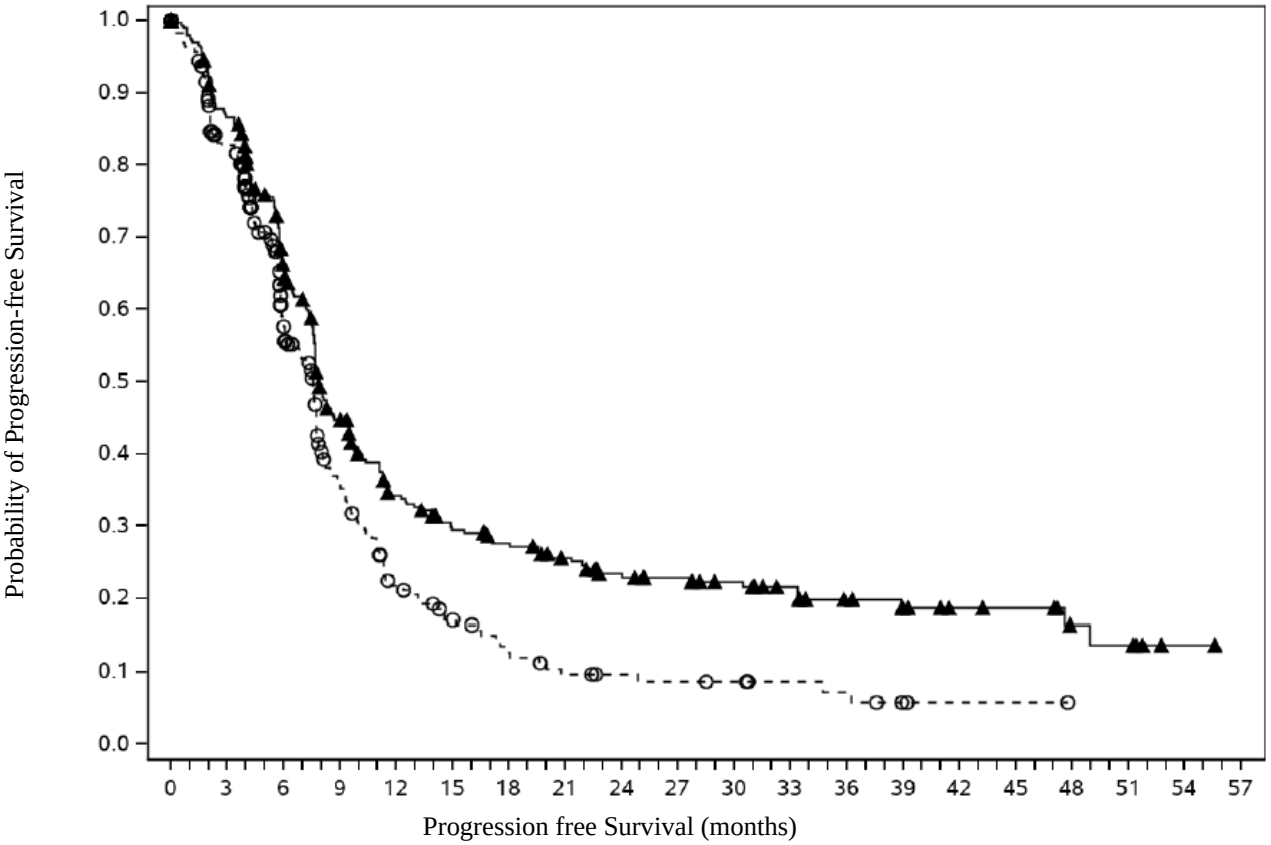
304 277 242 208 166 140 122 102 82 65 49 39 33 24 17 16 13 9 4 4 1 0

- - -▲- - - Nivolumab + gemcitabine-cisplatin chemotherapy (events: 172/304), median and 95% CI: 21.72 (18,63, 26.38)

- - -❍- - - Gemcitabine-cisplatin chemotherapy (events: 193/304), median and 95% CI: 18.85 (14.72, 22.44)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

Figure 25: Kaplan Meier curves of PFS (CA209901)



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy																				
304	253	179	116	82	65	57	49	41	36	31	26	19	14	11	10	10	6	5	1	0
Gemcitabine-cisplatin chemotherapy																				
304	223	119	63	35	25	17	12	12	10	9	8	6	5	2	1	1	0	0	0	0

- - -▲- - - Nivolumab + gemcitabine-cisplatin chemotherapy (events: 211/304), median and 95% CI: 7.92 (7.62, 9.49)

- - -❍- - - Gemcitabine-cisplatin chemotherapy (events: 191/304), median and 95% CI: 7.56 (6.05, 7.75)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

The primary analysis of PFS included censoring for new anti-cancer treatment before disease progression (Table 37). Results for PFS with and without censoring for new anti-cancer treatment before disease progression were consistent.

Open-label phase 2 study (CA209275)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma was evaluated in a phase 2, multicentre, open-label, single-arm study (CA209275).

The study included patients (18 years or older) who had disease progression during or following platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients that received more than 2 prior lines of chemotherapy with liver metastases were excluded.

A total of 270 patients who received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks with a minimum follow-up of 8.3 months were evaluable for efficacy. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first

tumour assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks thereafter up to 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit, did not have rapid disease progression, and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was ORR as determined by BICR. Additional efficacy measures included duration of response, PFS and OS.

The median age was 66 years (range: 38 to 90) with 55% ≥ 65 years of age and 14% ≥ 75 years of age. The majority of patients were white (86%) and male (78%). Baseline ECOG performance status was 0 (54%) or 1 (46%).

Table 38: Efficacy results (CA209275)[a]

	nivolumab (n = 270)	
Confirmed objective response	54 (20.0%)	
(95% CI)	(15.4, 25.3)	
Complete response (CR)	8 (3.0%)	
Partial response (PR)	46 (17.0%)	
Stable disease (SD)	60 (22.2%)	
Median duration of response[b]		
Months (range)	10.4 (1.9^+-12.0^+)	
Median time to response		
Months (range)	1.9 (1.6, 7.2)	
Progression-free survival		
Events (%)	216 (80)	
Median (95% CI) months	2.0 (1.9, 2.6)	
Rate (95% CI) at 6 months	26.1 (20.9, 31.5)	
Overall survival[c]		
Events (%)	154 (57)	
Median (95% CI) months	8.6 (6.05, 11.27)	
Rate (95% CI) at 12 months	41.0 (34.8, 47.1)	
	Tumour PD-L1 expression level	
	< 1%	**≥ 1%**
Confirmed objective response (95% CI)		
	16% (10.3, 22.7) n = 146	25% (17.7, 33.6) n = 124
Median duration of response Months (range)		
	10.4 (3.7, 12.0^+)	Not Reached (1.9^+, 12.0^+)
Progression-free survival		
Median (95% CI) months	1.9 (1.8, 2.0)	3.6 (1.9, 3.7)
Rate (95% CI) at 6 months	22.0 (15.6, 29.2)	30.8 (22.7, 39.3)
Overall survival		
Median (95% CI) months	5.9 (4.37, 8.08)	11.6 (9.10, NE)
Rate (95% CI) at 12 months	34.0 (26.1, 42.1)	49.2 (39.6, 58.1)

"$^+$" denotes a censored observation.

[a] median follow-up 11.5 months.

[b] Data unstable due to the limited duration of response.

[c] included 4 drug-related deaths: 1 pneumonitis, 1 acute respiratory failure, 1 respiratory failure, and 1 cardiovascular failure.

NE: non-estimable

Results from post-hoc, exploratory analyses indicate that in patients with low (e.g. <1%) to no tumour PD-L1 expression, other patient characteristics (e.g. liver metastases, visceral metastases, baseline haemoglobin <10g/dL and ECOG performance status = 1) might contribute to the clinical outcome.

Open-label phase 1/2 study (CA209032)
CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients (including 18 subjects who received planned crossover treatment with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg combination) with similar inclusion criteria to study CA209275 treated with nivolumab monotherapy 3 mg/kg for urothelial carcinoma. At a minimum follow-up of 9 months, investigator-assessed confirmed ORR was 24.4% (95% CI: 15.3, 35.4). The median duration of response was not reached (range: 4.4-16.6^{+} months). The median OS was 9.7 months (95% CI: 7.26, 16.16) and the estimated OS rates were 69.2% (CI: 57.7, 78.2) at 6 months and 45.6% (CI: 34.2, 56.3) at 12 months.

Adjuvant treatment of urothelial carcinoma

Randomised phase 3 study of adjuvant nivolumab vs. placebo (CA209274)
The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. The MIUC pathologic staging criteria that defines high risk patients was ypT2-ypT4a or ypN^{+} for adult patients who received neoadjuvant cisplatin chemotherapy, and pT3-pT4a or pN^{+} for adult patients who did not receive neoadjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. The study included patients regardless of their PD-L1 status, who had an ECOG performance status score of 0 or 1 (an ECOG PS of 2 was allowed for patients ineligible for neoadjuvant cisplatin chemotherapy). Tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. The study excluded patients with active, known or suspected autoimmune disease, patients who had treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

A total of 709 patients were randomised to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Of these, 282 patients had tumour cell PD-L1 expression ≥ 1%; 140 in the nivolumab arm and 142 in the placebo arm. Randomisation was stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression (≥ 1% vs. < 1%/indeterminate), and use of cisplatin neoadjuvant chemotherapy. Tumour imaging assessments were to be performed every 12 weeks from the date of first dose to week 96, then every 16 weeks from week 96 to week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years. The primary efficacy outcome measures were disease-free survival (DFS) in all randomised patients and DFS in randomised patients with tumour cell PD-L1 expression ≥ 1%. DFS was defined as the time between the date of randomisation and the date of the first documented recurrence assessed by investigator (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Secondary efficacy outcome measures included overall survival (OS).

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 66 years (range: 34 - 92 years), 76% were male and 76% were white. Eighty two percent had muscle invasive bladder cancer (MIBC), 18% had upper tract urothelial carcinoma (UTUC) (renal pelvis and ureter), 42% of patients received prior cisplatin in the neoadjuvant setting, 45% of patients were N+ at radical resection, patients had ECOG performance status of 0 (61%), 1 (37%), or 2 (2%), and 7% of patients had a haemoglobin < 10 g/dL.

At the primary pre-specified interim analysis in patients with tumour cell PD-L1 expression ≥ 1% (minimum follow-up of 6.3 months and median follow-up of 22.1 months for the nivolumab arm), the

study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab as compared to placebo. Median DFS as determined by the investigator was not reached (95% CI: 21.19, N.R.) for nivolumab versus 8.41 months (95% CI: 5.59, 21.19) for placebo, HR 0.55 (98.72% CI: 0.35, 0.85), p-value = 0.0005. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent.

In an updated descriptive DFS analysis in patients with tumour cell PD-L1 expression ≥ 1% (minimum follow-up of 11.4 months and median follow-up of 25.5 months for the nivolumab arm), DFS improvement was confirmed.

Efficacy results from this descriptive updated analysis are shown in Table 39 and Figure 26.

Table 39: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209274)

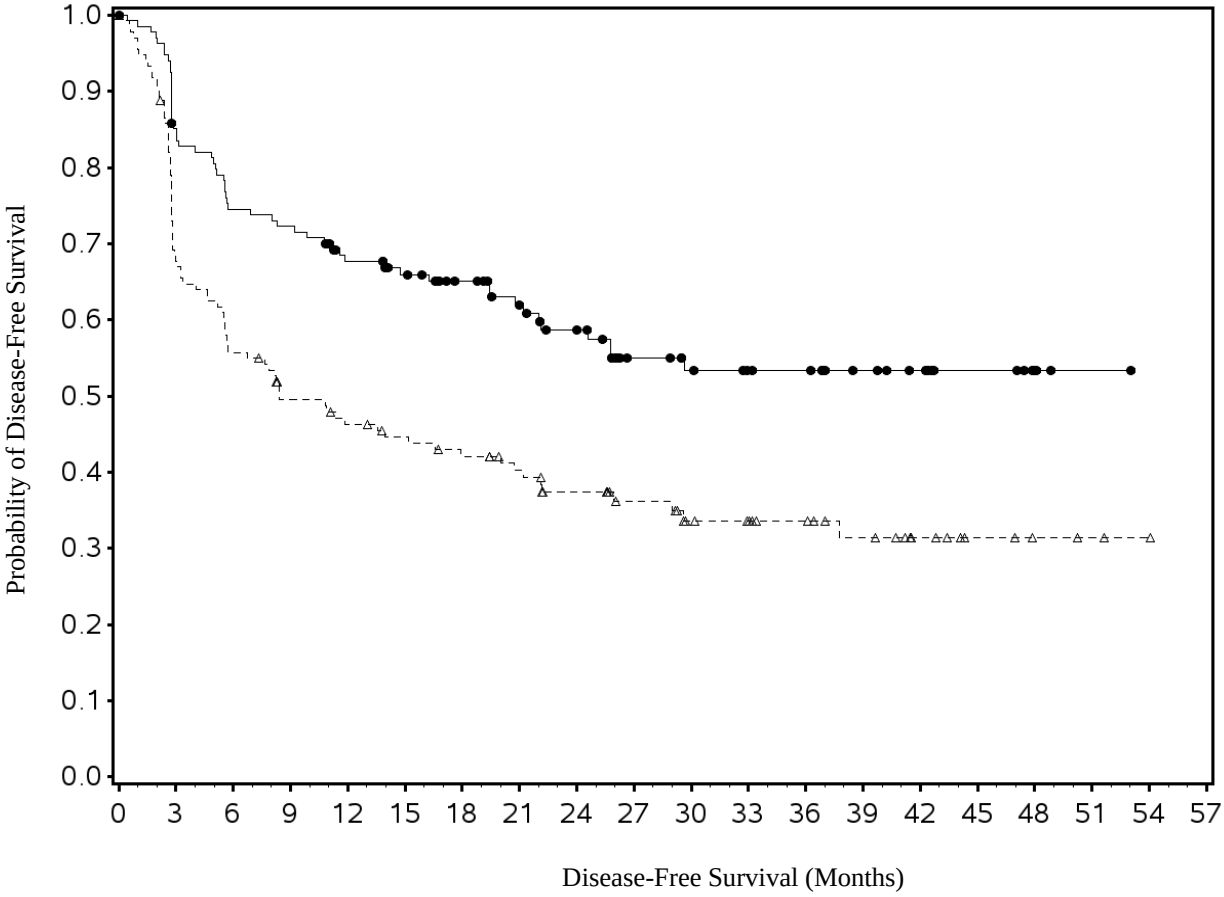
	nivolumab (n = 140)	**placebo** (n = 142)
Disease-Free Survival	Minimum follow-up 11.4 months	
Events (%)	56 (40.0)	85 (59.9)
Hazard ratio (95% CI)[a]	0.53 (0.38, 0.75)	
Median (95% CI) (months)[b]	NR (22.11, NE)	8.41 (5.59, 20.04)
Rate (95% CI) at 6 months	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)
Rate (95% CI) at 12 months	67.6 (59.0, 74.9)	46.3 (37.6, 54.5)
Rate (95% CI) at 24 months	58.6 (49.3, 66.9)	37.4 (29.0, 45.8)

NR: not reached, NE: non-estimable.

[a] Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.

[b] Based on Kaplan-Meier estimates.

Figure 26: Kaplan-Meier curves of DFS in patients with tumour cell PD-L1 expression ≥ 1% (CA209274)



Number of subjects at risk

Placebo																			
142	90	74	62	57	53	49	44	36	29	23	21	18	14	9	5	3	2	1	0
Nivolumab																			
140	113	99	96	85	75	67	58	50	38	33	30	29	22	19	8	3	1	0	0

- - -△- - - Placebo (events: 85/142), median and 95% CI: 8.41 (5.59, 20.04)
——■—— Nivolumab (events: 56/140), median and 95% CI: N.A. (22.11, N.A.)

Minimum follow-up of 11.4 months

Exploratory pre-specified subgroup descriptive analyses were performed in patients based on prior cisplatin treatment in the neoadjuvant setting.
In the subgroup of patients with tumour cell PD-L1 expression ≥ 1% who received prior cisplatin in the neoadjuvant setting (n = 118), the DFS HR was 0.37 (95% CI: 0.22, 0.64) with median DFS not reached and 8.41 months for the nivolumab and placebo arms, respectively. In the subgroup of patients with tumour cell PD-L1 expression ≥ 1% who did not receive prior cisplatin in the neoadjuvant setting (n = 164), the DFS HR was 0.69 (95% CI: 0.44, 1.08) with median DFS of 29.67 and 11.37 months for the nivolumab and placebo arms, respectively.

dMMR or MSI-H colorectal cancer

Open-label study of nivolumab in combination with ipilimumab versus chemotherapy in dMMR or MSI-H CRC patients naive to treatment in the metastatic setting
The safety and efficacy of nivolumab 240 mg in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or metastatic CRC with known tumour MSI-H or dMMR status were evaluated in a randomized, multi-arm, phase 3, open-label study (CA2098HW). Study treatment arms included nivolumab monotherapy, nivolumab in combination with ipilimumab, or investigator's

choice of chemotherapy. MSI-H or dMMR tumour status was determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumour specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary efficacy population. Patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors were excluded from the study. Randomisation was stratified by tumour location (right vs left). Patients randomized to the chemotherapy arm could receive nivolumab plus ipilimumab combination upon progression assessed by BICR.

A total of 303 previously untreated patients, in the metastatic setting, were randomised to study, including 202 patients to nivolumab in combination with ipilimumab and 101 patients to chemotherapy. Among them 255 had centrally confirmed MSI-H/dMMR status, 171 in the nivolumab in combination with ipilimumab arm and 84 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 240 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the chemotherapy arm received: mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus followed by fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for nivolumab in combination with ipilimumab up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

The baseline characteristics of all randomised previously untreated for metastatic disease patients were: the median age was 63 years (range: 21 to 87), with 46% ≥ 65 years of age and 18% ≥ 75 years of age; 46% were male and 86% were White. Baseline ECOG performance status was 0 (54%) and ≥ 1 (46%); tumour location was right-sided or left-sided for 68% and 32% of patients, respectively; and 39 patients had confirmed Lynch syndrome among the 223 patients with a known status. The baseline characteristics of previously untreated for metastatic disease patients with centrally confirmed MSI-H/dMMR were consistent with all randomised previously untreated patients. Among the 101 patients randomised to receive chemotherapy, 88 received chemotherapy per protocol, including oxaliplatin-containing regimens (58%) and irinotecan-containing regimens (42%). Additionally, 66 patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

A primary efficacy outcome measure of the study was BICR-assessed PFS per RECIST 1.1. Additional efficacy measures included ORR assessed by BICR, OS, and duration of response.

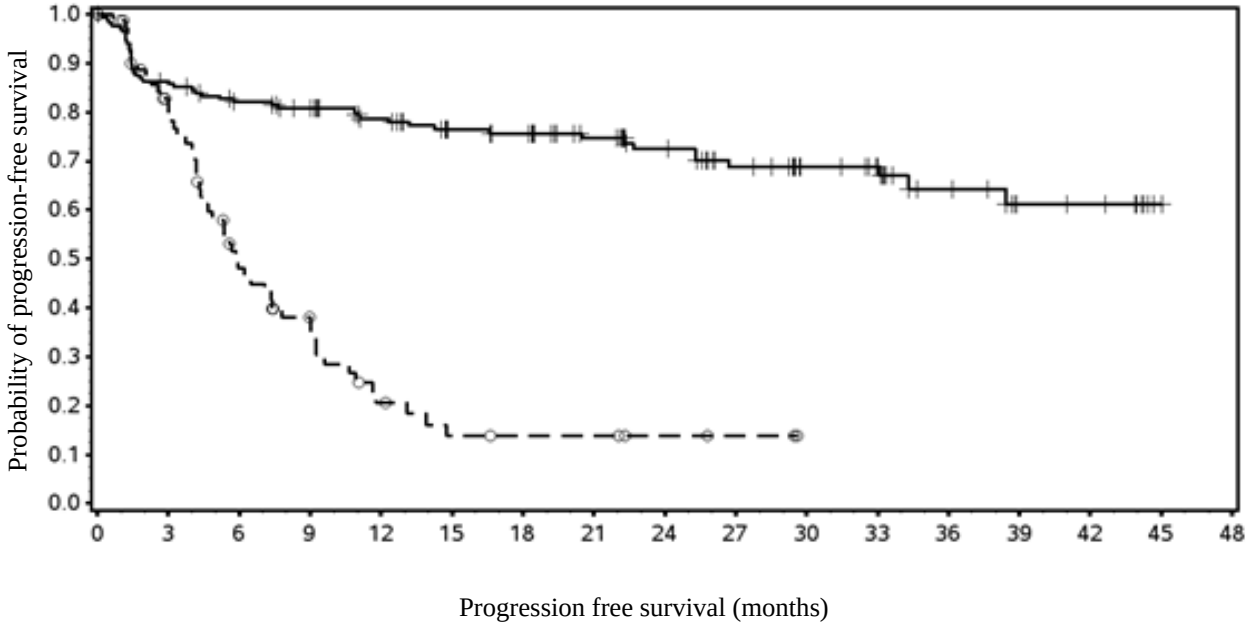
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 40 and Figure 27. At the time of this interim analysis, the other endpoints, including the data from nivolumab monotherapy arm, were not tested, due to testing hierarchy.

Table 40: Efficacy results in first-line MSI-H/dMMR centrally confirmed CRC (CA2098HW)[a]

	nivolumab + ipilimumab (n = 171)	chemotherapy (n = 84)
Progression-free survival		
Events	48 (28%)	52 (62%)
Hazard ratio	0.21	
95% CI	(0.14, 0.32)	
p-value[b]	< 0.0001	
Median (95% CI) (months)	NR (38.4, NR)	5.9 (4.4, 7.8)

a Median follow-up of 31.5 months (range: 6.1 to 48.4 months).
b Based on stratified 2-sided log-rank test

Figure 27: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Number of subjects at risk

Nivolumab + ipilimumab																
171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemotherapy																
84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

—+—— Nivolumab + ipilimumab (events: 48/171), median and 95% CI: N.A. (38.44, N.A.)
- - - ❍ - - - Chemotherapy (events: 52/84), median and 95% CI: 5.85 (4.37, 7.79)

Open-label study of nivolumab in combination with ipilimumab in dMMR or MSI-H CRC in patients who received prior fluoropyrimidine-based combination chemotherapy

The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of dMMR or MSI-H metastatic CRC was evaluated in a Phase 2, multi-centre, open-label, single-arm study (CA209142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan. Patients who had their most recent prior treatment in the adjuvant setting should have progressed on or within 6 months of completion of adjuvant chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients were treated with nivolumab 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary outcome measure was investigator-assessed ORR. Secondary outcome measures were BICR-assessed ORR and disease control rate. Analysis of ORR included duration of and time to response. Exploratory outcome measures included PFS and OS.

The median age was 58 years (range: 21-88) with 32% ≥ 65 years of age and 9% ≥ 75 years of age, 59% were male and 92% were white. Baseline ECOG performance status was 0 (45%) or 1 (55%), 25% of patients had BRAF mutations, 37% had KRAS mutations, and 12% were unknown. Of the 119 treated patients, 109 had received prior fluoropyrimidine based chemotherapy in the metastatic setting and 9 in the adjuvant setting. Before study enrolment, of the 119 treated patients, 118 (99%) had received fluorouracil, 111 (93%) had received oxaliplatin, 87 (73%) had received irinotecan as part of prior therapies; 82 (69%) had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Twenty three percent, 36%, 24%, and 16% received 1, 2, 3, or 4 or more prior therapies respectively, and 29% of patients had received an EGFR inhibitor.

Efficacy results (minimum follow-up 46.9 months; median follow-up 51.1 months) are shown in Table 41.

Table 41: Efficacy results (CA209142)*

	nivolumab + ipilimumab (n = 119)
Confirmed objective response, n (%)	77 (64.7)
(95% CI)	(55.4, 73.2)
Complete response (CR), n (%)	15 (12.6)
Partial response (PR), n (%)	62 (52.1)
Stable disease (SD), n (%)	25 (21.0)
Duration of response	
Median (range) months	NR (1.4, 58.0+)
Median time to response	
Months (range)	2.8 (1.1, 37.1)

* per investigator assessment
"+" denotes a censored observation.
NR = not reached

The BICR-assessed ORR was 61.3% (95% CI: 52.0, 70.1), including CR rate of 20.2% (95% CI: 13.4, 28.5), PR rate of 41.2% (95% CI: 32.2, 50.6) and stable disease reported in 22.7%. BICR assessments were generally consistent with the investigator assessment. Confirmed responses were observed regardless of BRAF or KRAS mutation status, and tumour PD-L1 expression levels.

Of 119 patients 11 (9.2%) patients were ≥ 75 years. The investigator assessed ORR in patients ≥ 75 years was 45.5% (95% CI: 16.7, 76.6).

Oesophageal squamous cell carcinoma

Randomised phase 3 study of nivolumab monotherapy in previously treated patients (ONO-4538-24/ CA209473)

The safety and efficacy of nivolumab 240 mg monotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) was evaluated in a phase 3 randomised active-controlled, open-label study (ONO-4538-24/CA209473). The study included adult patients (20 years or older) who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based combination regimen, and patients were enrolled regardless of

tumour PD-L1 expression level. Patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had active autoimmune disease, medical conditions requiring systemic immunosuppression, and patients with apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), were excluded from the study.

A total of 419 patients were randomised 1:1 to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n = 210) or investigator's choice of taxane chemotherapy: either docetaxel (n = 65) 75 mg/m^2 intravenously every 3 weeks, or paclitaxel (n = 144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off. Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases (≤ 1 vs. ≥ 2) and tumour PD-L1 expression (≥ 1% vs. <1% or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 65 years (range: 33-87), 53% were ≥ 65 years of age, 10% were aged ≥ 75 years, 87% were male, 96% were Asian and 4% were white. Baseline ECOG performance status was 0 (50%) or 1 (50%).

With a minimum follow-up of 17.6 months, the study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice taxane chemotherapy. Efficacy results are shown in Table 42 and Figure 28.

A higher proportion of patients experienced death within the first 2.5 months in the nivolumab arm (32/210, 15.2%) as compared to the chemotherapy arm (15/209, 7.2%). No specific factor(s) associated with early deaths could be identified.

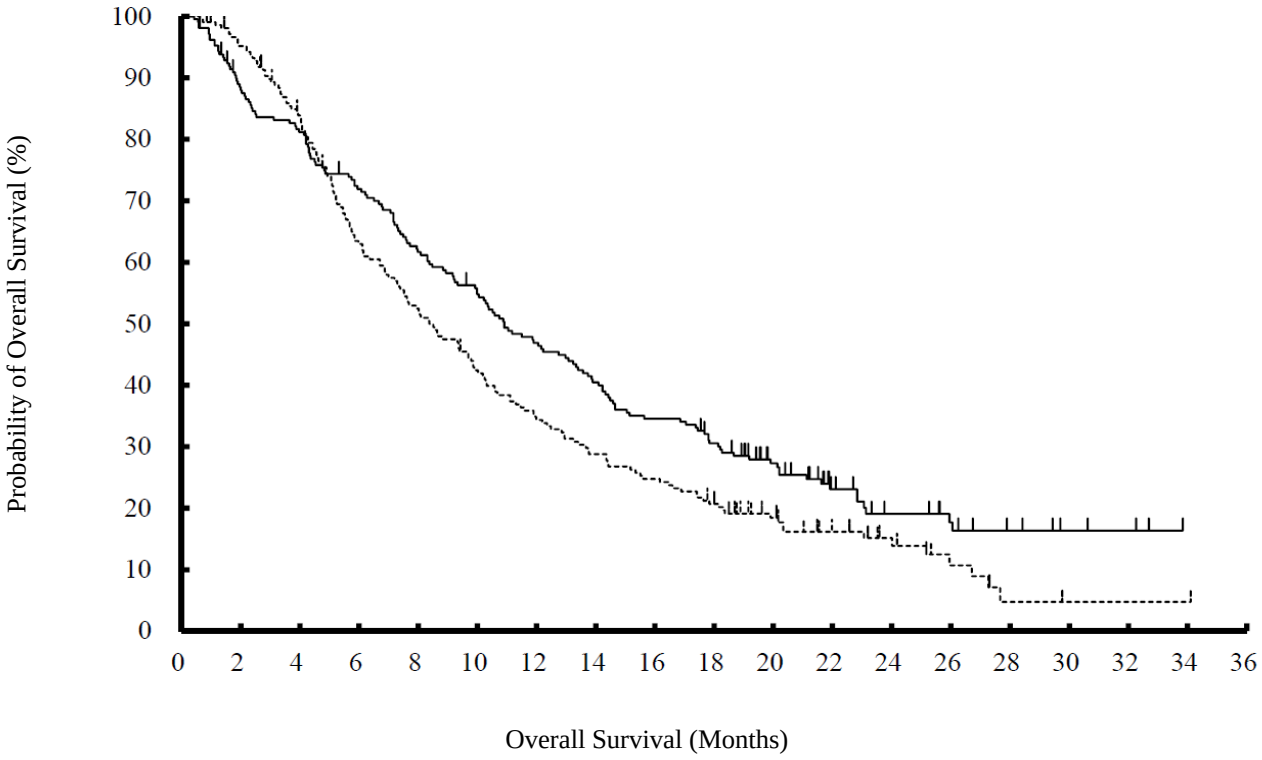
Table 42: Efficacy results (ONO-4538-24/CA209473)

	nivolumab (n = 210)	**investigator's choice (n = 209)**
Overall Survival[a]		
Events	160 (76%)	173 (83%)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Median (95% CI) (months)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Objective Response Rate[d,e]	33 (19.3%)	34 (21.5%)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response	1 (0.6%)	2 (1.3%)
Partial response	32 (18.7%)	32 (20.3%)
Stable disease	31 (18.1%)	65 (41.1%)
Median duration of response (95% CI) (months)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
Progression-Free Survival[a]		
Events	187 (89%)	176 (84%)
Median (95% CI) (months)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	

[a] Based on ITT analysis.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.

[d] Based on Response Evaluable Set (RES) analysis, n=171 in nivolumab group and n=158 in investigator's choice group.
[e] Not significant, p-value 0.6323.

Figure 28: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)



Number of subjects at risk

Nivolumab																		
210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Investigator's choice																		
209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

———— Nivolumab - - - - - - Investigator's choice

Of the 419 patients, 48% had tumour PD-L1 expression ≥ 1%. The remaining 52% of patients had tumour PD-L1 expression <1%. The hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the nivolumab and investigator's choice taxane chemotherapy arms, respectively, in the tumour PD-L1 positive subgroup. In the tumour PD-L1 negative OSCC subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the nivolumab and chemotherapy arms, respectively.

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy and nivolumab in combination with chemotherapy vs. chemotherapy as first-line treatment (CA209648)
The safety and efficacy of nivolumab in combination with ipilimumab and nivolumab in combination with chemotherapy were evaluated in a randomised, active-controlled, open-label study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic OSCC. Patients were enrolled regardless of their tumour PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of oesophagus, not amenable to chemoradiation and/or surgery. Prior adjuvant, neoadjuvant, or definitive chemotherapy, radiotherapy or chemoradiotherapy was permitted if given as part of curative intent regimen prior to trial enrollment. Patients who had a baseline performance score ≥ 2, had brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the study. Randomisation was stratified by tumour cell

PD-L1 status (≥ 1% vs. < 1% or indeterminate), region (East Asia vs. rest of Asia vs. rest of world), ECOG performance status (0 vs. 1), and number of organs with metastases (≤ 1 vs. ≥ 2).

A total of 970 patients were randomised to receive either nivolumab in combination with ipilimumab, (n = 325), nivolumab in combination with chemotherapy (n = 321), or chemotherapy (n = 324). Of these, 473 patients had tumour cell PD-L1 expression ≥ 1%,158 in the nivolumab plus ipilimumab arm, 158 in the nivolumab plus chemotherapy arm, and 157 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks, and patients in the nivolumab plus chemotherapy arm received nivolumab 240 mg every 2 weeks on days 1 and 15, fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Patients in the chemotherapy arm received fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Treatment continued until disease progression, unacceptable toxicity, or up to 24 months. Patients in the nivolumab plus ipilimumab arm who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Patients in the nivolumab plus chemotherapy arm in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued.

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 63 years (range: 26-85), 8.2% were ≥ 75 years of age, 81.8% were male, 73.1% were Asian, and 23.3% were white. Patients had histological confirmation of squamous cell carcinoma (98.9%) or adenosquamous cell carcinoma (1.1%) in the oesophagus. Baseline ECOG performance status was 0 (45.2%) or 1 (54.8%).

Nivolumab in combination with ipilimumab vs. chemotherapy

The primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with tumour cell PD-L1 expression ≥ 1%. Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 13.1 months, the study demonstrated a statistically significant improvement in OS in patients with tumour cell PD-L1 expression ≥ 1%. Efficacy results are shown in Table 43.

Table 43: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

	nivolumab + ipilimumab (n = 158)	**chemotherapy[a] (n = 157)**
Overall survival		
Events	106 (67.1%)	121 (77.1%)
Hazard ratio (98.6% CI)[b]	0.64 (0.46, 0.90)	
p-value[c]	0.0010	
Median (95% CI) (months)[d]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	57.1 (49.0, 64.4)	37.1 (29.2, 44.9)
Progression-free survival[e]		
Events	123 (77.8%)	100 (63.7%)
Hazard ratio (98.5% CI)[b]	1.02 (0.73, 1.43)	
p-value[c]	0.8958	
Median (95% CI) (months)[d]	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months[d]	26.4 (19.5, 33.9)	10.5 (4.7, 18.8)

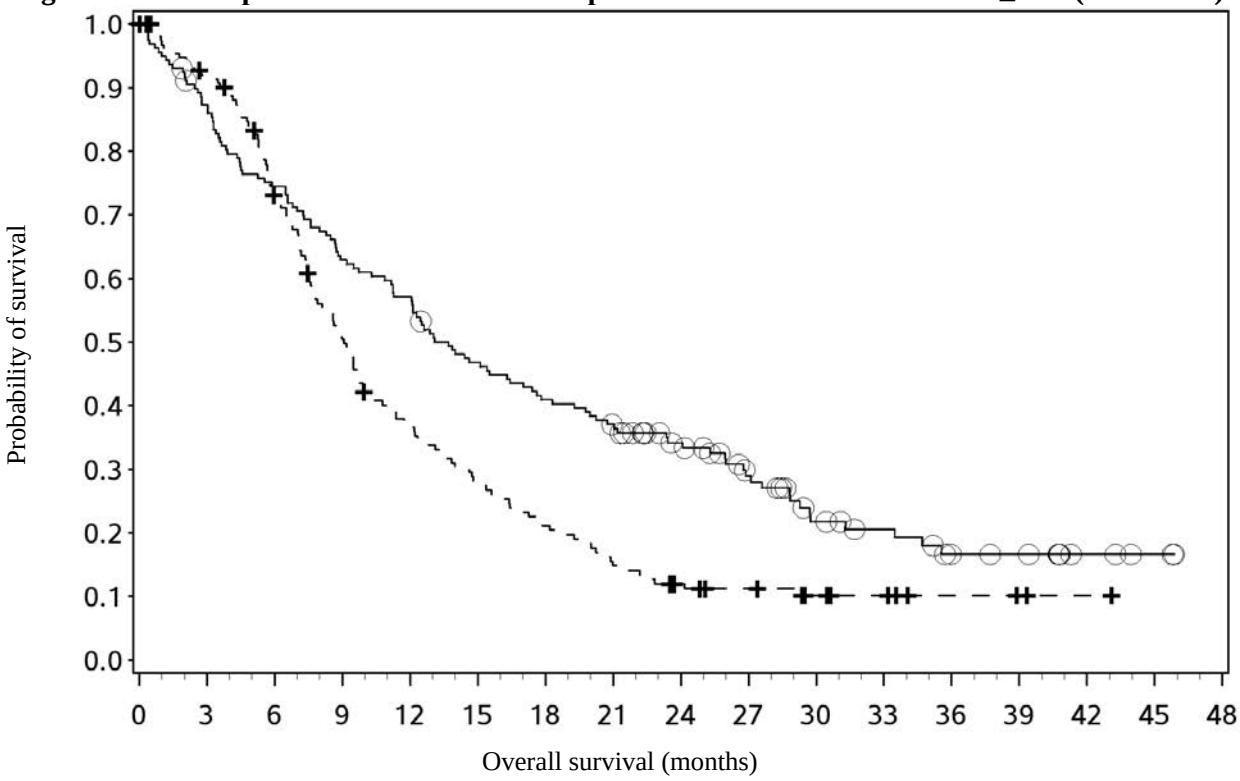
	nivolumab + ipilimumab (n = 158)	chemotherapy[a] (n = 157)
Overall response rate, n (%)[e]	56 (35.4)	31 (19.7)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)
Complete response	28 (17.7)	8 (5.1)
Partial response	28 (17.7)	23 (14.6)
Duration of response[e]		
Median (95% CI) (months)[d]	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)
Range	1.4^{+}, 34.5^{+}	1.4^{+}, 31.8^{+}

[a] Fluorouracil and cisplatin.
[b] Based on stratified Cox proportional hazard model.
[c] Based on stratified 2-sided log-rank test.
[d] Based on Kaplan-Meier estimates.
[e] Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 13.70 months (95% CI: 11.24, 17.41) for nivolumab plus ipilimumab vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.63; 95% CI: 0.49, 0.82). Median PFS was 4.04 months (95% CI: 2.40, 4.93) for nivolumab plus ipilimumab vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 1.02; 95% CI: 0.77, 1.34). The ORR was 35.4% (95% CI: 28.0, 43.4) for nivolumab plus ipilimumab vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.

The Kaplan-Meier curves for OS with a minimum follow-up of 20 months are shown in Figure 29.

Figure 29: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



Number of subjects at risk

Nivolumab + ipilimumab																
158	136	116	98	89	72	63	55	43	31	20	16	10	9	4	2	0
Chemotherapy																
157	137	107	73	53	40	30	21	15	12	8	6	3	2	1	0	0

—❍—— Nivolumab + ipilimumab (events: 119/158), median and 95% CI: 13.70 (11.24, 17.41)
- - - + - - - Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)
Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Nivolumab in combination with chemotherapy vs. chemotherapy

The primary efficacy outcome measures were PFS (by BICR) and OS in patients with tumour cell PD-L1 expression ≥ 1%. Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 12.9 months the study demonstrated a statistically significant improvement in OS and PFS in patients with tumour cell PD-L1 expression ≥ 1%. Efficacy results are shown in Table 44.

Table 44: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

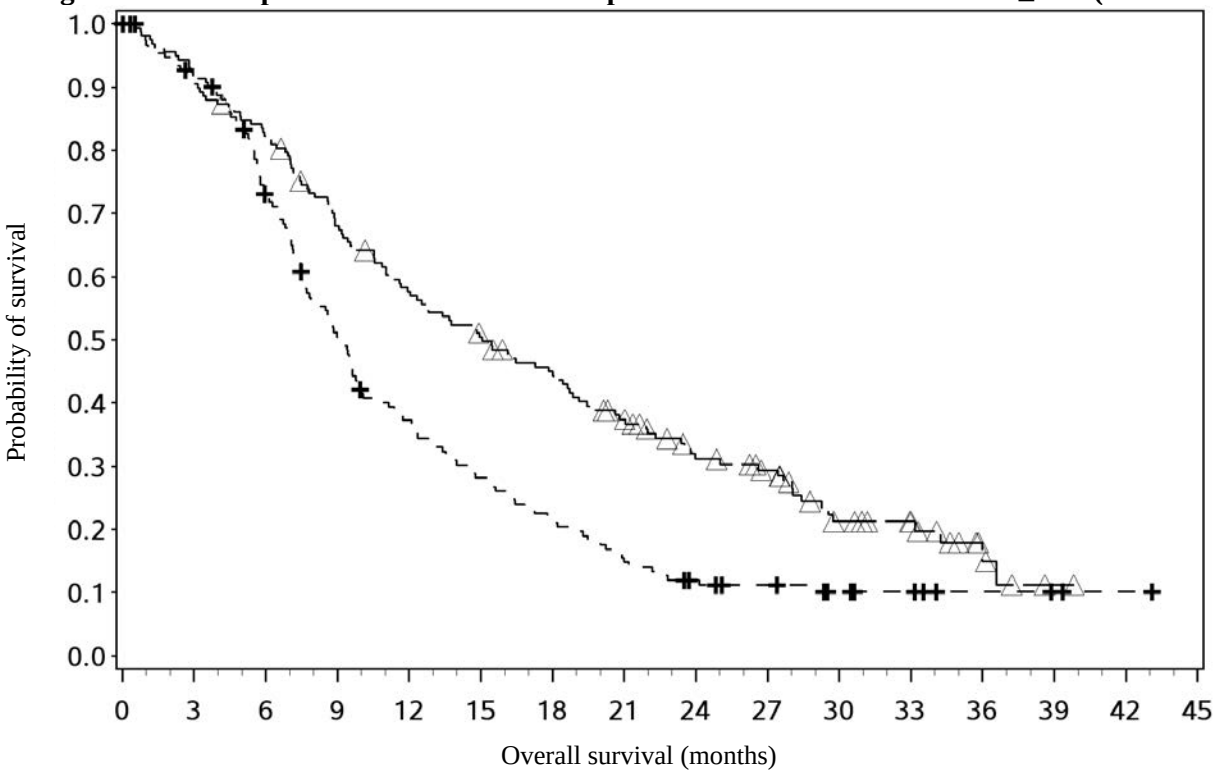
	nivolumab + chemotherapy (n = 158)	**chemotherapy[a] (n = 157)**
Overall survival		
Events	98 (62.0%)	121 (77.1%)
Hazard ratio (99.5% CI)[b]	0.54 (0.37, 0.80)	
p-value[c]	<0.0001	
Median (95% CI) (months)[d]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	58.0 (49.8, 65.3)	37.1 (29.2, 44.9)

	nivolumab + chemotherapy (n = 158)	chemotherapy[a] (n = 157)
Progression-free survival[e]		
Events	117 (74.1%)	100 (63.7%)
Hazard ratio (98.5% CI)[b]	0.65 (0.46, 0.92)	
p-value[c]	0.0023	
Median (95% CI) (months)[d]	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months[d]	25.4 (18.2, 33.2)	10.5 (4.7, 18.8)
Overall response rate, n (%)[e]	84 (53.2)	31 (19.7)
(95% CI)	(45.1, 61.1)	(13.8, 26.8)
Complete response	26 (16.5)	8 (5.1)
Partial response	58 (36.7)	23 (14.6)
Duration of response[e]		
Median (95% CI) (months)[d]	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)
Range	1.4^{+}, 34.6	1.4^{+}, 31.8^{+}

[a] Fluorouracil and cisplatin.
[b] Based on stratified Cox proportional hazard model.
[c] Based on stratified 2-sided log-rank test.
[d] Based on Kaplan-Meier estimates.
[e] Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 15.05 months (95% CI: 11.93, 18.63) for nivolumab plus chemotherapy vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.59; 95% CI: 0.46, 0.76). Median PFS was 6.93 months (95% CI: 5.68, 8.35) for nivolumab plus chemotherapy vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 0.66; 95% CI: 0.50, 0.87). The ORR was 53.2% (95% CI: 45.1, 61.1) for nivolumab plus chemotherapy vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.
The Kaplan-Meier curves for OS and PFS with a minimum follow-up of 20 months are shown in Figures 30 and 31.

Figure 30: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



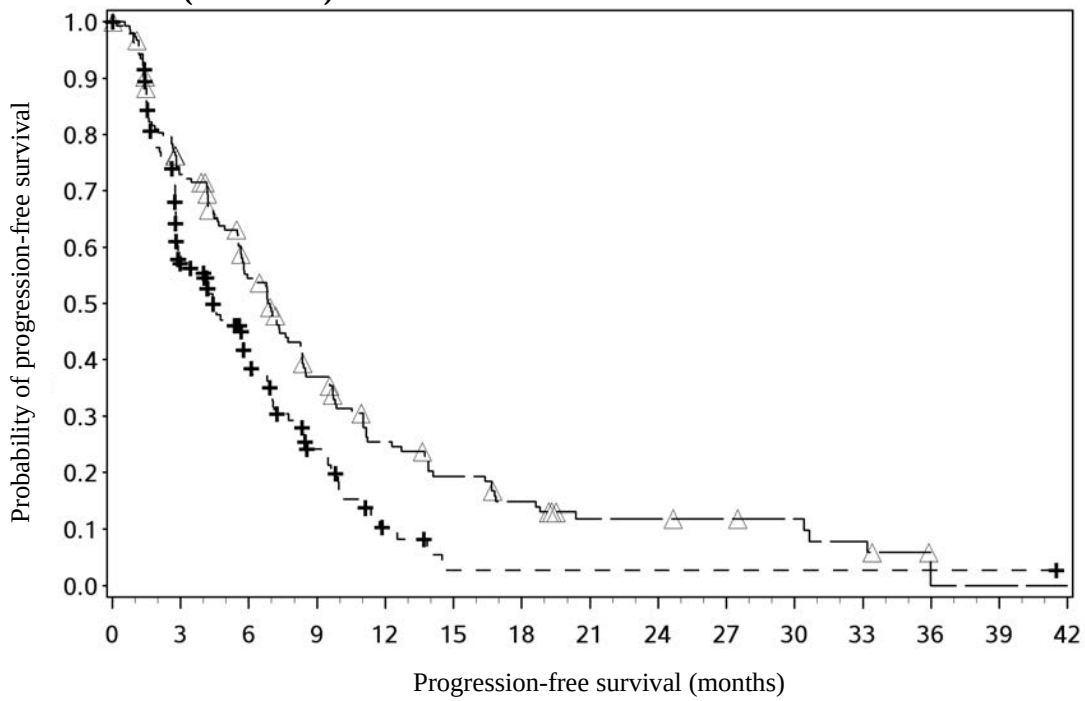
Number of subjects at risk

Nivolumab + chemotherapy															
158	143	129	105	88	76	66	52	38	32	19	15	5	1	0	0
Chemotherapy															
157	137	107	73	53	40	30	21	15	12	8	6	3	2	1	0

- - -△- - - Nivolumab + chemotherapy (events: 118/158), median and 95% CI: 15.05 (11.93, 18.63)
- - -+- - - Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Figure 31: Kaplan-Meier curves of PFS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



Number of subjects at risk

Nivolumab + chemotherapy														
158	107	75	47	30	22	16	10	10	7	6	4	0	0	0
Chemotherapy														
157	68	36	17	5	1	1	1	1	1	1	1	1	1	0

- - -△- - - Nivolumab + chemotherapy (events: 123/158), median and 95% CI: 6.93 (5.65, 8.35)
- - -+- - - Chemotherapy (events: 101/157), median and 95% CI: 4.44 (2.89, 5.82)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209577). The study included adult patients who had received CRT, followed by complete surgical resection of carcinoma within 16 weeks prior to randomisation, and who had residual pathologic disease as confirmed by the investigator, with at least ypN1 or ypT1. Patients with a baseline performance score ≥ 2, who did not receive concurrent CRT prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were enrolled regardless of tumour PD-L1 expression level.

A total of 794 patients were randomised 2:1 to receive either nivolumab 240 mg (n = 532) or placebo (n = 262). Patients were administered nivolumab intravenously over 30 minutes every 2 weeks for 16 weeks followed by 480 mg infused over 30 minutes every 4 weeks beginning at week 17. Patients were administered placebo over 30 minutes with the same dosing schedule as nivolumab. Randomisation was stratified by tumour PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). Treatment continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. The primary efficacy outcome measure was disease-free survival (DFS), as assessed by the investigator, defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant from the primary resected site) or death from any cause, whichever occurred first. Patients on treatment underwent imaging for tumour recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 26-86) with 36% ≥ 65 years of age and 5% ≥ 75 years of years. The majority of patients were white (82%) and male (85 %). Baseline ECOG performance status was 0 (58%) or 1 (42%).

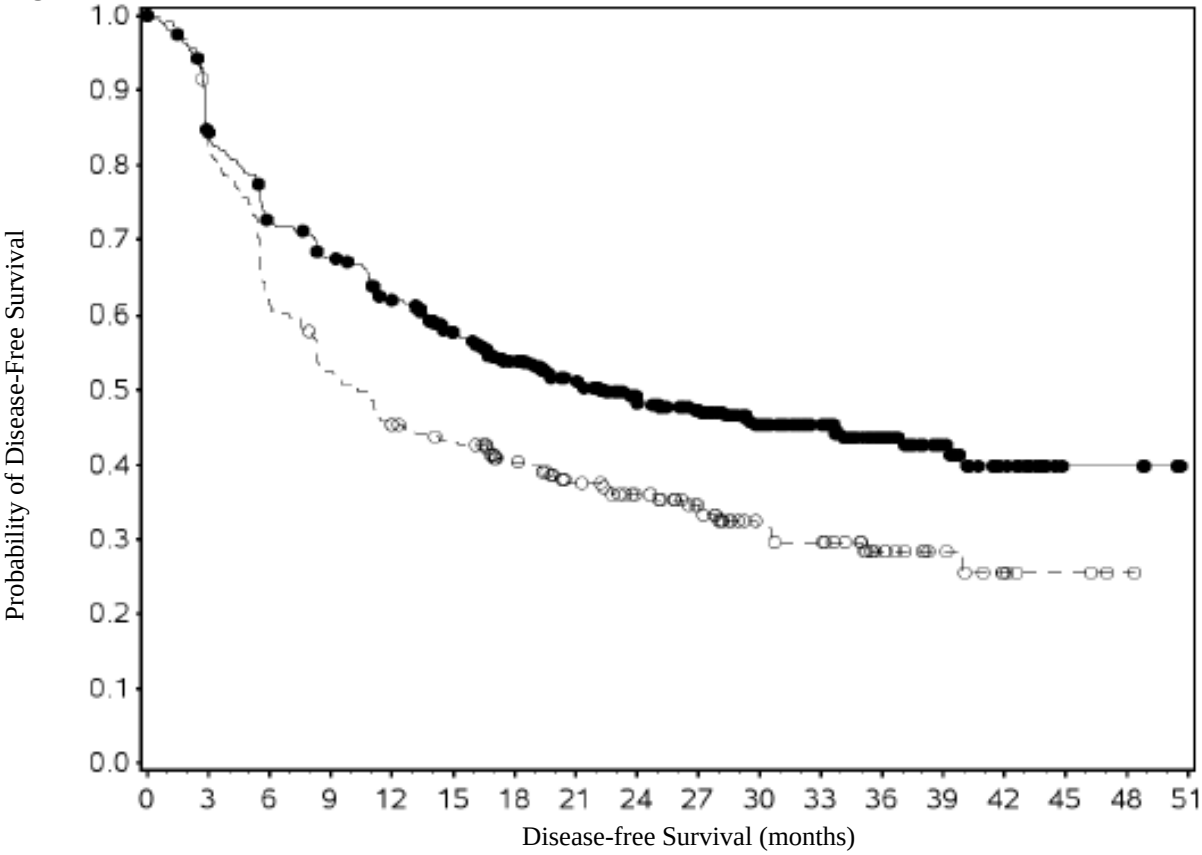
At the primary pre-specified interim analysis (minimum of 6.2 months and a median of 24.4 months follow-up), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab compared with placebo. Median DFS as determined by the investigator was 22.41 months (95% CI: 16.62, 34.00) for nivolumab versus 11.04 months (95% CI: 8.34, 14.32) for placebo, HR 0.69 (96.4% CI: 0.56, 0.86), p-value < 0.0003. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent. In an updated descriptive DFS analysis with minimum of 14 months and median of 32.2 months follow-up, DFS improvement was confirmed. Efficacy results from this descriptive secondary analysis are shown in Table 45 and Figure 32.

Table 45: Efficacy results (CA209577)

	nivolumab (n = 532)	**placebo (n = 262)**
Disease-free Survival[a] with minimum follow-up 14 months[c]		
Events (%)	268 (50)	171 (65)
Hazard ratio (95% CI)[b]	0.67 (0.55, 0.81)	
Median (95% CI) (months)	22.4 (17.0, 33.6)	10.4 (8.3, 13.9)
Rate (95% CI) at 6 months	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)
Rate (95% CI) at 12 months	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
Rate (95% CI) at 24 months	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)

[a] Based on all randomised patients.
[b] Based on a stratified cox proportional hazards model.
[c] Descriptive analysis based on data cut-off: 18-Feb-2021.

Figure 32: Kaplan-Meier curves of DFS (CA209577)



Number of subjects at risk

Nivolumab																	
532	433	371	342	307	272	228	194	160	137	106	84	57	34	19	4	4	0
Placebo																	
262	211	158	134	114	107	88	73	62	50	33	30	18	11	5	3	1	0

—■— Nivolumab (events: 268/532), median and 95% CI: 22.41 (16.95, 33.64)

- - -○- - - Placebo (events: 171/262), median and 95% CI: 10.35 (8.31, 13.93)

Based on data cut-off: 18-Feb-2021, minimum follow-up of 14 months

DFS benefit was observed regardless of histology and PD-L1 expression.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy (dose and schedule of nivolumab selected depending on the chemotherapy regimen used, see below) was evaluated in a phase 3, randomised, open-label study (CA209649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. Patients were enrolled regardless of their tumour cell PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. A retrospective re-scoring of a patient's tumour PD-L1 status using CPS was conducted using the PD-L1-stained tumour specimens used for randomisation. Patients with known HER2-positive tumours, who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, or who had active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. A total of 643 patients with HER2-undetermined status (40.3% of the study population) were included in the study. Randomisation was stratified by tumour cell PD-L1 status (≥ 1% vs. < 1% or indeterminate), region (Asia vs. US vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy regimen. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy or chemotherapy. Of these, 955 patients had PD-L1 CPS ≥ 5; 473 in the nivolumab plus chemotherapy arm and 482 in the chemotherapy arm. Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 intravenously on day 1 and fluorouracil 1200 mg/m^2 intravenously by continuous infusion over 24 hours daily or per local standard on days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m^2 intravenously on day 1 and capecitabine 1000 mg/m^2 orally twice daily on days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks up to 24 months after treatment initiation. Tumour assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

Baseline characteristics were generally balanced across treatment groups. In patients with PD-L1 CPS ≥ 5, the median age was 62 years (range: 18-90), 11% were ≥ 75 years of age, 71% were male, 25% were Asian and 69% were white. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumour locations were distributed as gastric (70%), GEJ (18%) and oesophagus (12%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 CPS ≥ 5 based on the PD-L1 IHC 28-8 pharmDX. Secondary endpoints per the pre-specified hierarchical testing were OS in patients with PD-L1 CPS ≥ 1 and in all randomised patients; further endpoints included ORR (BICR) in PD-L1 CPS ≥ 5 and all randomised patients. At the primary pre-specified analysis, with a minimum follow-up of 12.1 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with PD-L1 CPS ≥ 5. Median OS was 14.4 months (95% CI: 13.1, 16.2) for nivolumab in combination with chemotherapy vs. 11.1 months (95% CI: 10.0, 12.1) for chemotherapy (HR = 0.71; 98.4% CI: 0.59, 0.86; p-value <0.0001). Median PFS was 7.69 months (95% CI: 7.03, 9.17) for nivolumab in combination with chemotherapy vs. 6.05 months (95% CI: 5.55, 6.90) for chemotherapy (HR = 0.68; 98% CI: 0.56, 0.81; p-value <0.0001). The ORR was 60% (95% CI: 55, 65) for nivolumab in combination with chemotherapy vs. 45% (95% CI: 40, 50) for chemotherapy.

At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 46, and Figures 33, and 34.

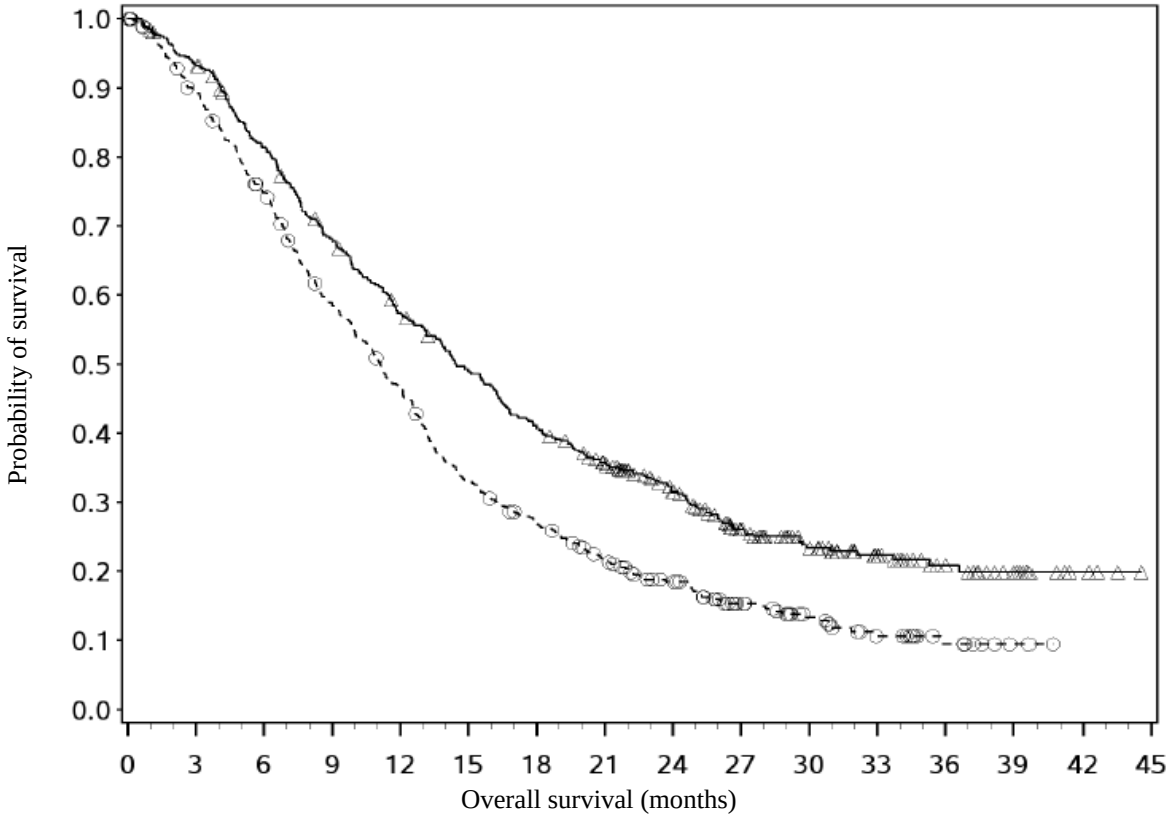
Table 46: Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

	nivolumab + chemotherapy (n = 473)	**chemotherapy (n = 482)**
	Minimum follow-up 19.4 months[a]	
Overall survival		
Events	344 (73%)	397 (82%)
Hazard ratio (95% CI)[b]	0.69 (0.60, 0.81)	
Median (95% CI) (months)[c]	14.4 (13.1, 16.3)	11.1 (10.0, 12.1)
Rate (95% CI) at 12 months	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)
Progression-free survival[d]		
Events	342 (72.3%)	366 (75.9%)
Hazard ratio (95% CI)[b]	0.68 (0.59, 0.79)	
Median (95% CI) (months)[c]	8.31 (7.03, 9.26)	6.05 (5.55, 6.90)
Rate (95% CI) at 12 months	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Objective response rate, n[d,e]	227/378 (60%)	176/390 (45%)
(95% CI)	(54.9, 65.0)	(40.1, 50.2)
Complete response	12.2%	6.7%
Partial response	47.9%	38.5%
Duration of response[d,e]		
Median (95% CI) (months)[c]	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)

[a] Descriptive analysis based on data cut-off: 04-Jan-2021.
[b] Based on stratified long Cox proportional hazard model.
[c] Kaplan-Meier estimate.
[d] Confirmed by BICR.
[e] Based on patients with measurable disease at baseline.

Figure 33: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)

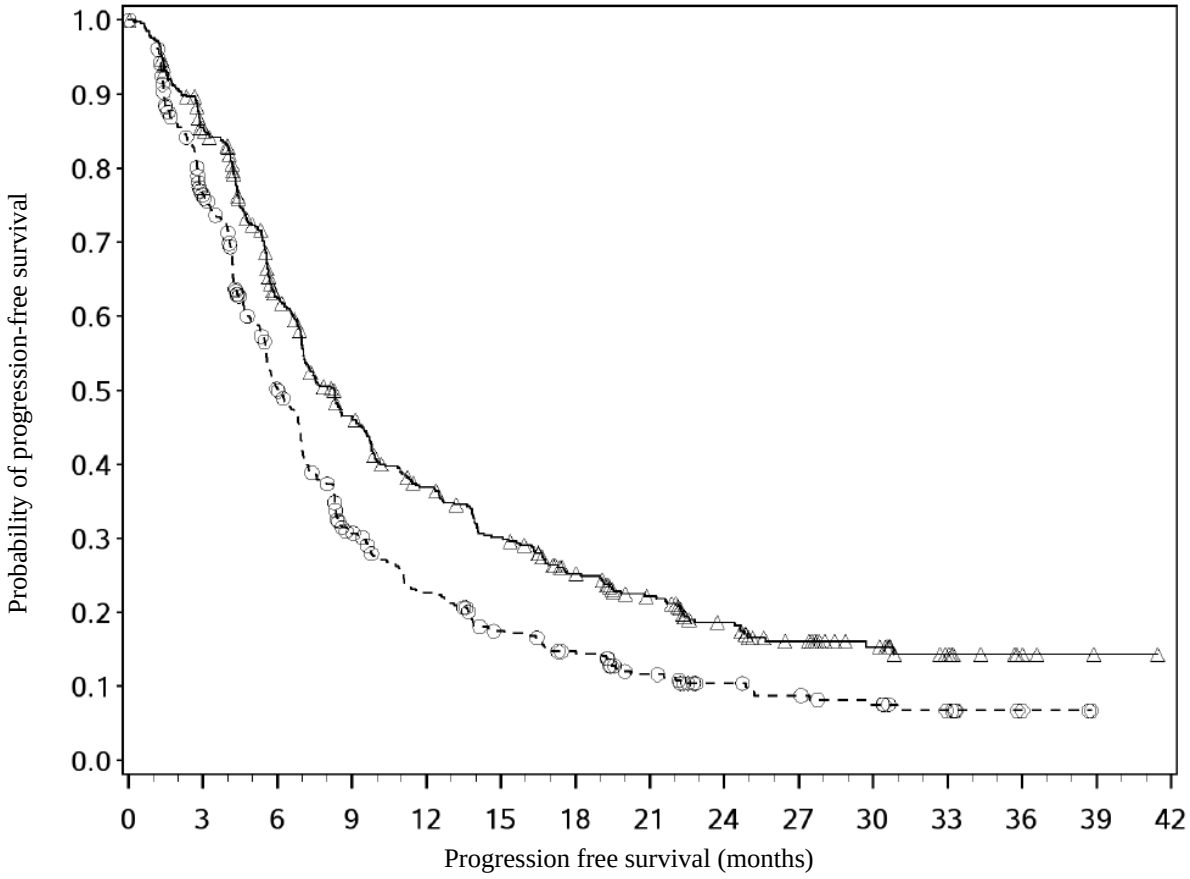


Number of subjects at risk

Nivolumab + chemotherapy															
473	439	378	314	263	223	187	155	118	78	56	37	23	13	4	0
Chemotherapy															
482	421	350	272	213	152	122	92	68	44	28	16	8	2	0	0

—△—— Nivolumab + chemotherapy (events: 344/473), median and 95% CI: 14.42 (13.14, 16.26)
- - -○- - - Chemotherapy (events: 397/482), median and 95% CI: 11.10 (10.02, 12.09)
Minimum follow-up of 19.4 months

Figure 34: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥ 5 (CA209649)



Number of subjects at risk

Nivolumab + chemotherapy														
473	386	259	186	143	115	88	67	47	31	20	11	4	1	0
Chemotherapy														
482	328	202	114	81	58	46	30	20	16	12	7	3	0	0

—△—— Nivolumab + chemotherapy (events: 342/473), median and 95% CI: 8.31 (7.03, 9.26)
- - -❍- - - Chemotherapy (events: 397/482), median and 95% CI: 6.05 (5.55, 6.90)
Minimum follow-up of 19.4 months

Hepatocellular carcinoma

The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or advanced hepatocellular carcinoma (HCC) were evaluated in a phase 3, randomised, active-controlled, open-label study (CA2099DW). The study included adult patients (18 years or older) with histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrolment. The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies. Prior neo-adjuvant or adjuvant systemic therapy was permitted. Patients with active autoimmune disease, brain or leptomeningeal metastases, prior liver transplant, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV) were excluded from the study. Randomisation was stratified by aetiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥ 400 or < 400 ng/mL).

A total of 668 patients were randomised to receive nivolumab in combination with ipilimumab (n = 335) or investigator's choice (n = 333) of lenvatinib or sorafenib. In the investigator's choice arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. Patients in the nivolumab plus ipilimumab arm received nivolumab 1 mg/kg every 3 weeks in combination with ipilimumab 3 mg/kg every 3 weeks, for up to a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the investigators' choice arm received either lenvatinib 8 mg orally daily (if body weight < 60 kg) or 12 mg orally daily (if body weight ≥ 60 kg), or sorafenib 400 mg orally twice daily. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments were conducted at baseline, after randomisation at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy.

Baseline characteristics were generally balanced across treatment groups. The median age was 66 years (range: 20 to 89), with 53% ≥ 65 years and 16% ≥ 75 years, 53% were White, 44% were Asian, 2.2% were Black, and 82% were male. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection. Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and ≥ 7 were 77%, 20%, and 3%, respectively. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥ 400 µg/L.

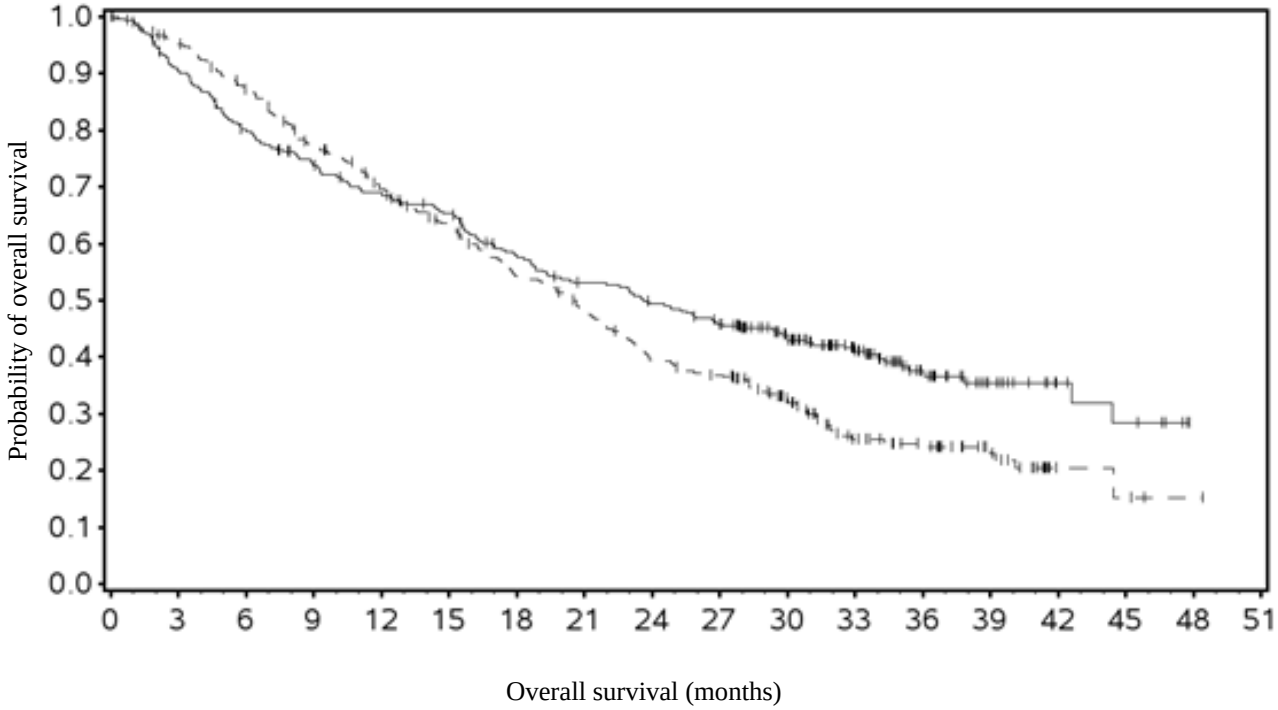
The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to nivolumab in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 47 and Figure 35.

Table 47: Efficacy results in first-line HCC (CA2099DW)[a]

	nivolumab + ipilimumab (n = 335)	**lenvatinib or sorafenib (n = 333)**
Overall survival		
Events	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI)[b]	0.79 (0.65, 0.96)	
p-value[c]	0.0180	
Overall Response Rate, n (%)[d]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[e]	< 0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[d]		
Median (95% CI)	30.4 (21.2, N.A.)	12.9 (10.2, 31.2)

[a] Minimum follow-up of 26.8 months. Median follow up of 35.2 months.
[b] Based on stratified Cox proportional hazard model.
[c] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤ 0.0257.
[d] Assessed by BICR using RECIST 1.1.
[e] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤ 0.025.

Figure 35: Kaplan-Meier curve of OS in first-line patients with HCC (CA2099DW)



Number of subjects at risk

Nivolumab + ipilimumab																	
335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
Investigator's choice																	
333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

—+—— Nivolumab + ipilimumab (events: 194/335), median and 95% CI: 23.66 (18.33, 29.44)
- - -+- - - Lenvatinib or sorafenib (events: 228/333), median and 95% CI: 20.63 (17.48, 22.54)

Paediatric population

Open label phase 1/2 study (CA209070)
Study CA209070 was an open-label, single-arm, dose-confirmation and dose-expansion, phase 1/2 study of nivolumab as a single agent and in combination with ipilimumab in paediatric and young adult patients with recurrent or refractory solid or haematological tumours, including neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, advanced melanoma, cHL and non-Hodgkin lymphoma (NHL). Among the 126 treated patients, 97 were paediatric patients from 12 months to < 18 years of age. Of the 97 paediatric patients, 64 were treated with nivolumab monotherapy (3 mg/kg administered intravenously over 60 minutes every 2 weeks) and 33 were treated with nivolumab in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks). Patients received either nivolumab as monotherapy for a median of 2 doses (range: 1, 89) or nivolumab in combination with ipilimumab for a median of 2 doses (range: 1, 24). The main primary outcome measures were safety, tolerability and antitumour activity as evaluated by descriptive ORR and OS.

Among the 64 paediatric patients treated with nivolumab monotherapy, 60 were response-evaluable patients (melanoma n = 1, solid tumours n = 47 and haematological tumours n = 12). In the 48 response-evaluable paediatric patients with melanoma or solid tumours, no objective responses were observed. In the 12 response-evaluable paediatric patients with haematological tumours, ORR was 25.0% (95% CI: 5.5, 57.2), including 1 complete response in cHL and 2 partial responses, one in cHL and another one in NHL. In the descriptive analyses for the 64 paediatric patients treated with nivolumab monotherapy, the median OS was 6.67 months (95% CI: 5.98, NA); 6.14 months

(95% CI: 5.39, 24.67) for patients with melanoma or solid tumours, and not reached for patients with haematological tumours.

Among the 30 response-evaluable paediatric patients treated with nivolumab in combination with ipilimumab (solid tumours other than melanoma only), no objective responses were observed. For the 33 paediatric patients treated with nivolumab in combination with ipilimumab, the median OS was 8.25 months (95% CI: 5.45, 16.95) in a descriptive analysis.

Open label phase 1b/2 study (CA209908)
Study CA209908 was an open-label, sequential-arm, phase 1b/2 clinical study of nivolumab monotherapy and nivolumab in combination with ipilimumab in paediatric and young adult patients with high-grade primary CNS malignancies, including diffuse intrinsic pontine glioma (DIPG), high-grade glioma, medulloblastoma, ependymoma and other recurrent subtypes of high-grade CNS malignancy (e.g., pineoblastoma, atypical teratoid/rhabdoid tumour, and embryonal CNS tumours). Of the 151 paediatric patients (from ≥ 6 months to < 18 years old) enrolled in the study, 77 were treated with nivolumab monotherapy (3 mg/kg every 2 weeks) and 74 were treated with nivolumab in combination with ipilimumab (3 mg/kg nivolumab followed by 1 mg/kg ipilimumab, every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks). The primary efficacy outcome measures were OS in the DIPG cohort and investigator-assessed PFS, based on RANO criteria, for all other tumour types. The median OS in the DIPG cohort was 10.97 months (80% CI: 9.92, 12.16) in patients treated with nivolumab monotherapy and 10.50 months (80% CI: 9.10, 12.32) in patients treated with nivolumab in combination with ipilimumab. For all other studied CNS paediatric tumour types, the median PFS ranged from 1.23 to 2.35 months in patients treated with nivolumab monotherapy and from 1.45 to 3.09 months in patients treated with nivolumab in combination with ipilimumab. There were no objective responses observed in the study with the exception of one ependymoma patient treated with nivolumab monotherapy who had a partial response. Results for OS, PFS, and ORR observed in study CA209908 do not suggest clinically meaningful benefit over what may be expected in these patient populations.

The European Medicines Agency has deferred the obligation to submit the results of studies with nivolumab in all subsets of the paediatric population in the treatment of malignant neoplasms of lymphoid tissue (see section 4.2 for information on paediatric use).

Safety and efficacy in elderly patients

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population. Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population. Data from MPM patients showed a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively).

5.2 Pharmacokinetic properties

Nivolumab monotherapy

The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 7.9 mL/h, 25.0 days, and 86.6 μg/mL, respectively, based on a population PK analysis.

Nivolumab CL in cHL patients was approximately 32% lower relative to NSCLC. Nivolumab baseline CL in adjuvant melanoma patients was approximately 40% lower and steady state CL approximately 20% lower relative to advanced melanoma. With available safety data, these decreases in CL were not clinically meaningful.

The metabolic pathway of nivolumab has not been characterised. Nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Nivolumab in combination with ipilimumab

When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29% and the CL of ipilimumab was increased by 9%, which was not considered clinically relevant. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab was increased by 1% and the CL of ipilimumab was decreased by 1.5%, which were not considered clinically relevant.

When administered in combination with ipilimumab, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies and the CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies. These changes were not considered clinically relevant.

Nivolumab in combination with ipilimumab and chemotherapy

When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and with 2 cycles of chemotherapy, the CL of nivolumab decreased approximately 10% and the CL of ipilimumab increased approximately 22%, which were not considered clinically relevant.

Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumour type, tumour size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful.

Paediatric population
For nivolumab monotherapy, the exposures of nivolumab in adolescents 12 years of age and older who weigh at least 50 kg are expected to be comparable to those in adult patients at the recommended dose. Body weight-based dosing is recommended for adolescents 12 years of age and older who weigh less than 50 kg.

For nivolumab in combination with ipilimumab, the exposures of nivolumab and ipilimumab in adolescents 12 years of age and older are expected to be comparable to those in adult patients at the recommended dose.

Renal impairment
The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 m^2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m^2; n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with different tumour types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, GC, and cHL) with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 351) and in patients with moderate hepatic impairment (total bilirubin > 1.5 × to 3 × ULN and any AST; n = 10) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 3096) in a population PK analysis. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate

hepatic impairment and normal hepatic function. Similar results were observed in patients with HCC (mild hepatic impairment: n = 152; moderate hepatic impairment: n = 13). Nivolumab has not been studied in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, foetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response and immune-related disorders have been reported in PD-1 knockout mice.

Fertility studies have not been performed with nivolumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Sodium chloride
Mannitol (E421)
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80 (E433)
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. OPDIVO should not be infused concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

Unopened vial

3 years

After preparation of infusion

Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	**Chemical and physical in-use stability**	
	Storage at 2ºC to 8ºC protected from light	**Storage at room temperature (≤ 25°C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	8 hours (of total 7 days storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature (≤ 25°C). Aseptic handling should be ensured during the preparation of infusion (see section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

For storage conditions after preparation of the infusion, see section 6.3.

6.5 Nature and contents of container

4 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a dark blue flip-off seal (aluminium). Pack size of 1 vial.
10 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a grey flip-off seal (aluminium). Pack size of 1 vial.
12 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a blue flip-off seal (aluminium). Pack size of 1 vial.
24 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a red matte flip-off seal (aluminium). Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Preparation and administration

Calculating the dose
More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

Nivolumab monotherapy
The prescribed dose for the adult patient is 240 mg or 480 mg given regardless of body weight depending on indication (see section 4.2).

Melanoma (advanced or adjuvant treatment) in adolescents. The prescribed dose for adolescents 12 years of age and older weighing at least 50 kg is 240 mg or 480 mg. For adolescents 12 years of age and older and weighing less than 50 kg, the prescribed dose is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of OPDIVO concentrate to prepare the dose (mL) = the total nivolumab dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

Nivolumab in combination with ipilimumab
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given (please see above).

Nivolumab in combination with ipilimumab in MPM
The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in advanced colorectal cancer
The prescribed dose for the patient can be based on body weight (3 mg/kg) or can be 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in OSCC
The prescribed dose for the patient can be based on body weight (3 mg/kg) or 360 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in resectable NSCLC
The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in OSCC
The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma
The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab and chemotherapy
The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with cabozantinib
The prescribed dose for the patient is nivolumab 240 mg or 480 mg given regardless of body weight.

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion.

OPDIVO can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

OPDIVO concentrate may be diluted with either:

- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

STEP 1

- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial

if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.

Administer the OPDIVO infusion intravenously over a period of 30 or 60 minutes depending on the dose.

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm).

OPDIVO infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Disposal
Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001
EU/1/15/1014/002
EU/1/15/1014/003
EU/1/15/1014/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015
Date of latest renewal: 23 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 600 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 120 mg of nivolumab.
One vial of 5 mL contains 600 mg of nivolumab.

Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear to opalescent, colourless to yellow liquid, essentially free of visible particulates. The solution has a pH of 5.5-6.5 and an osmolality of 296-444 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults (see section 4.2).

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1).

Non-small cell lung cancer (NSCLC)

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Renal cell carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see sections 4.2 and 5.1).

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1).

Squamous cell cancer of the head and neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1).

Urothelial carcinoma

OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (see sections 4.2 and 5.1).

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Adjuvant treatment of urothelial carcinoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:
- first-line treatment of unresectable or metastatic colorectal cancer (see sections 4.2 and 5.1);
- treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (see sections 4.2 and 5.1).

Oesophageal squamous cell carcinoma (OSCC)

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (see section 5.1).

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Patients currently receiving intravenous nivolumab monotherapy, or in combination with chemotherapy or cabozantinib, may transition to OPDIVO solution for injection.

PD-L1 testing

If specified in the indication, patient selection for treatment with OPDIVO based on the tumour expression of PD-L1 should be assessed by a CE-marked in vitro IVD medical device test. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

MSI/MMR testing

If specified in the indication, patient selection for treatment with OPDIVO based on MSI-H/dMMR tumour status should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

Posology

OPDIVO as monotherapy
The recommended dose of OPDIVO solution for injection is either nivolumab 600 mg every 2 weeks **or** 1200 mg every 4 weeks (see section 5.1).

If patients need to be switched from the 600 mg every 2 weeks schedule to the 1200 mg every 4 weeks schedule, the first 1200 mg dose should be administered two weeks after the last 600 mg dose. Conversely, if patients need to be switched from the 1200 mg every 4 weeks schedule to the 600 mg every 2 weeks schedule, the first 600 mg dose should be administered four weeks after the last 1200 mg dose.

OPDIVO in combination with ipilimumab

Melanoma
Intravenous administration - OPDIVO combination phase
The recommended dose of OPDIVO solution for infusion is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously over 30 minutes every 3 weeks for the first 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks (see section 5.1). For the monotherapy phase, the first dose of nivolumab should be administered;
- 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 600 mg every 2 weeks; or
- 6 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 1200 mg every 4 weeks.

Renal cell carcinoma
Intravenous administration - OPDIVO combination phase
The recommended dose of OPDIVO solution for infusion is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 3 weeks for the first 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered;
- 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 600 mg every 2 weeks; or
- 6 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 1200 mg every 4 weeks.

dMMR or MSI-H colorectal cancer

First-line treatment of dMMR or MSI-H CRC
Intravenous administration - OPDIVO combination phase
The recommended dose is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is 600 mg every 2 weeks **or** 1200 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Treatment of dMMR or MSI-H CRC after prior first-line fluoropyrimidine-based combination chemotherapy
Intravenous administration - OPDIVO combination phase
The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab.

OPDIVO in combination with cabozantinib

Renal cell carcinoma
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks in combination with 40 mg cabozantinib administered orally every day.

OPDIVO in combination with chemotherapy

Oesophageal squamous cell carcinoma
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks administered in combination with fluoropyrimidine- and platinum-based chemotherapy (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The recommended dose of OPDIVO solution for injection is 600 mg in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

First-line treatment of unresectable or metastatic urothelial carcinoma
Intravenous administration - OPDIVO combination phase
The recommended dose of OPDIVO solution for infusion is 360 mg administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is 600 mg every 2 weeks **or** 1200 mg every 4 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

Duration of treatment
Treatment with OPDIVO, either as a monotherapy or in combination with other therapeutic agents, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).

For adjuvant therapy, the maximum treatment duration with OPDIVO is 12 months.

For OPDIVO in combination with cabozantinib, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the Summary of Product Characteristics (SmPC) for cabozantinib.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 1. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. When nivolumab is administered in combination with other therapeutic agents, refer to the SmPC of these other combination therapeutic agents regarding dosing.

Table 1: Recommended treatment modifications for OPDIVO or OPDIVO in combination

Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	OPDIVO+ipilimumab[a]	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment

Immune-related adverse reaction	Severity	Treatment modification
Immune-related hepatitis **NOTE:** for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[c]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

[a] During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs.

[b] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

[c] The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

OPDIVO as monotherapy or in combination with other therapeutic agents should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also package leaflet).

When OPDIVO is administered intravenously in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the intravenous combination treatment or OPDIVO monotherapy administered intravenously or subcutaneously could be resumed based on the evaluation of the individual patient.

When OPDIVO is administered in combination with chemotherapy, refer to the SmPC of the other combination therapy agents regarding dosing. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.

OPDIVO in combination with cabozantinib in RCC
When OPDIVO is used in combination with cabozantinib, the above treatment modifications in Table 1 also apply to the OPDIVO component. In addition, for liver enzyme elevations, in patients with RCC being treated with OPDIVO in combination with cabozantinib:

- If ALT or AST > 3 times ULN but ≤ 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with cabozantinib, refer to cabozantinib SmPC.
- If ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered.

Special populations

Paediatric population
The safety and efficacy of OPDIVO solution for injection in children below 18 years of age have not been established.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years).

Renal impairment
Based on the population pharmacokinetic (PK) results for intravenous nivolumab, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
Based on the population PK results for intravenous nivolumab, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Method of administration

OPDIVO solution for injection is for subcutaneous use
It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being administered to the patient as prescribed.

OPDIVO solution for injection is not intended for intravenous administration and must be given by subcutaneous injection only using the doses specified. More than one vial of OPDIVO solution for injection may be needed to give the total dose for the patient. For instructions on use and handling of the OPDIVO solution for injection before administration, see section 6.6.

Administer the full contents of the syringe of OPDIVO solution for injection into the subcutaneous tissue of the abdomen or thigh over a period of 3 to 5 minutes. The dose should not be split between two syringes or between two sites of administration. Alternate injection sites for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration of OPDIVO solution for injection is interrupted, it can be resumed at the same site, or at an alternate site.

During the treatment course with OPDIVO solution for injection, other medicinal products for subcutaneous administration should preferably be injected at different sites.

OPDIVO solution for infusion (intravenous formulation)
The Summary of Product Characteristics (SmPC) of OPDIVO concentrate for solution for infusion should be referred to for information on dosing instructions and method of administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Assessment of PD-L1 status
When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

Assessment of MSI/MMR status
When assessing the MSI-H and dMMR status of the tumour, it is important that a well-validated and robust methodology is used.

Immune-related adverse reactions
When nivolumab is administered in combination, refer to the SmPC of the other combination therapy agents prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Immune-related adverse reactions have occurred at similar frequencies when OPDIVO was administered in combination with cabozantinib relative to nivolumab monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the OPDIVO component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).

Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Cardiac and pulmonary adverse reactions including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions (see section 4.2).

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Immune-related pneumonitis
Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related colitis
Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of corticosteroid-refractory immune-related colitis is confirmed addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

For Grade 4 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Nivolumab monotherapy should be withheld for Grade 3 diarrhoea or colitis, and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued. Grade 3 diarrhoea or colitis observed with nivolumab in combination with ipilimumab requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related hepatitis
Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related nephritis and renal dysfunction
Severe nephritis and renal dysfunction have been observed with monotherapy treatment or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 or 3 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related endocrinopathies
Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

For symptomatic hypothyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld and antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, nivolumab or nivolumab in combination with ipilimumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic Grade 2 or 3 hypophysitis, nivolumab or nivolumab in combination with ipilimumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, nivolumab or nivolumab in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions
Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy (see section 4.8). Nivolumab or nivolumab in combination with ipilimumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of SJS and TEN some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab or nivolumab in combination with ipilimumab should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab or nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended (see section 4.2).

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions
The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis, and myelitis. Cases of Vogt-Koyanagi-Harada syndrome, hypoparathyroidism, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.

The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see section 4.2).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.

Cases of acute graft-versus-host disease (GVHD) and transplant related mortality (TRM) have been observed from the follow-up of patients with classical Hodgkin lymphoma undergoing allogeneic haematopoietic stem cell transplant (HSCT) after previous exposure to intravenous nivolumab. Careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case-by-case. In patients treated with intravenous nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients.

Infusion reactions (intravenous formulation)
Severe infusion reactions have been reported in clinical trials of intravenous nivolumab or intravenous nivolumab in combination with ipilimumab (see section 4.8). In case of a severe or life-threatening infusion reaction, the intravenous nivolumab or intravenous nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive intravenous nivolumab or intravenous nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Disease-specific precautions

Advanced melanoma
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of nivolumab or nivolumab in combination with ipilimumab (see sections 4.5 and 5.1). Patients with ocular/uveal melanoma were excluded from pivotal clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). Patients with baseline performance score of 2, treated leptomeningeal metastases, ocular/uveal melanoma, autoimmune disease and patients who have had a Grade 3-4 adverse reaction that was related to prior anti-CTLA-4 therapy were included in study CA209172 (see section 5.1). In the absence of data for patients who had been receiving systemic immunosuppressants prior to study entry, and for patients with active brain or leptomeningeal metastases, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1 ≥ 1%). Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see sections 4.8 and 5.1).

Use of nivolumab in melanoma patients with rapidly progressing disease
Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with rapidly progressing disease (see section 5.1).

Adjuvant treatment of melanoma
There are no data on adjuvant treatment in patients with melanoma with the following risk factors (see sections 4.5 and 5.1):

- patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications,
- patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation),
- patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways),
- subjects under the age of 18 years.

In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Non-small cell lung cancer

Treatment of NSCLC after prior chemotherapy
Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of NSCLC (see sections 4.5 and 5.1). Patients with baseline performance score of 2 were included in study CA209171 (see section 5.1). In the absence of data for patients with autoimmune disease, symptomatic interstitial lung disease, active brain metastases and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see section 5.1).

Renal cell carcinoma

Nivolumab or nivolumab in combination with ipilimumab
Patients with any history of concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab or nivolumab in combination with ipilimumab (see sections 4.5 and 5.1). In the absence of data, nivolumab or nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Nivolumab in combination with cabozantinib
Patients with any active brain metastases, autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab in combination with cabozantinib (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with cabozantinib should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

When nivolumab is given with cabozantinib, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to nivolumab monotherapy in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the SmPC for cabozantinib).

Head and neck cancer
Patients with a baseline performance score ≥ 2, active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites were excluded from the SCCHN clinical trial (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

Urothelial carcinoma

Treatment of advanced urothelial carcinoma
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Adjuvant treatment of urothelial carcinoma
Patients with a baseline performance score of ≥ 2 (except patients with a baseline performance score of 2 who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy), evidence of disease after surgery, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial of adjuvant treatment of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

dMMR or MSI-H colorectal cancer
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial in dMMR or MSI-H metastatic CRC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Oesophageal squamous cell carcinoma

First-line treatment of OSCC
Patients with a baseline performance score ≥ 2, any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Treatment of OSCC after prior first-line chemotherapy
The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).

Patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with OSCC. A higher number of deaths within 2.5 months after randomisation was observed with nivolumab compared to chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer
Patients with a baseline performance score ≥ 2, who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in oesophageal and gastro-oesophageal junction cancer (see sections 4.5 and 5.1). In the absence of data,

nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
Patients who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in gastric, GEJ or oesophageal adenocarcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Study CA209649 excluded patients with known HER2-positive status. Patients with undetermined status were allowed in the study and represented 40.3% of patients (see section 5.1).

OPDIVO contains polysorbate 80 (E433)
This medicinal product contains 2.5 mg of polysorbate 80 in each 5 mL vial which is equivalent to 5 mg/10 mL. Polysorbates may cause allergic reactions.

Patient alert card
All prescribers of OPDIVO must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of OPDIVO therapy with the patient. The patient will be provided with the patient alert card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

Other forms of interaction

Systemic immunosuppression
The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of nivolumab in pregnant women. Studies in animals have shown embryofoetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

Breast-feeding

It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from

nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies to evaluate the effect of nivolumab on fertility have not been performed. Thus, the effect of nivolumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Nivolumab or nivolumab in combination with ipilimumab may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

4.8 Undesirable effects

Nivolumab as monotherapy (see section 4.2)

Summary of the safety profile
In the pooled dataset of nivolumab as monotherapy administered intravenously across tumour types (n = 4646) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (44%), musculoskeletal pain (28%), diarrhoea (26%), rash (24%), cough (22%), nausea (22%), pruritus (19%), decreased appetite (17%), arthralgia (17%), constipation (16%), dyspnoea (16%), abdominal pain (15%), upper respiratory tract infection (15%), pyrexia (13%), headache (13%), anaemia (13%) and vomiting (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 44%, with 0.3% fatal adverse reactions attributed to study drug. With a minimum of 63 months follow-up in NSCLC, no new safety signals were identified.

The safety of nivolumab administered subcutaneously was similar to the known safety profile of the intravenous formulation of nivolumab, with an additional adverse reaction of injection site reaction (7% in the subcutaneous nivolumab arm (n = 247) vs 0% in the intravenous nivolumab arm (n = 245)).

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4646) are presented in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia[a], bronchitis
Rare	aseptic meningitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	lymphopaenia[b], anaemia[b,i], leucopoenia[b], neutropaenia[a,b], thrombocytopaenia[b]
Uncommon	eosinophilia
Not known	haemophagocytic lymphohistiocytosis

Immune system disorders	
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis
Not known	solid organ transplant rejection[f]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency[j], hypopituitarism, hypophysitis, diabetes mellitus
Rare	diabetic ketoacidosis, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia[b]
Common	dehydration, weight decreased, hypoglycaemia[b]
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome[g]
Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,k], optic neuritis
Not known	myelitis (including transverse myelitis)
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Not known	Vogt-Koyanagi-Harada syndrome[f]
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis[a], pericardial disorders[h], arrhythmia (including ventricular arrhythmia)
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnoea[a], cough
Common	pneumonitis[a], pleural effusion
Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis[a], stomatitis, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer, pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders	
Uncommon	hepatitis, cholestasis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	psoriasis, rosacea, erythema multiforme, urticaria
Rare	toxic epidermal necrolysis[a, d], Stevens-Johnson syndrome[a]
Not known	lichen sclerosus[g], other lichen disorders

Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e], arthralgia
Common	arthritis
Uncommon	polymyalgia rheumatica
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a], rhabdomyolysis[a,d]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a]
Rare	tubulointerstitial nephritis, cystitis noninfective
General disorders and administration site conditions	
Very common	fatigue, pyrexia
Common	pain, chest pain, oedema[l], injection site reaction[m]
Investigations[b]	
Very common	increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypercalcaemia
Common	increased total bilirubin, hypernatraemia, hypermagnesaemia

Adverse reaction frequencies presented in Table 2 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease.

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

[c] Rash is a composite term which includes rash maculopapular, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash vesicular, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

[d] Reported also in studies outside the pooled dataset. The frequency is based on the programme-wide exposure.

[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.

[f] Post-marketing event (also see section 4.4).

[g] Reported in clinical studies and in the post-marketing setting.

[h] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.

[i] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.

[j] Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency.

[k] Includes encephalitis and limbic encephalitis.

[l] Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling.

[m] Reported in a study outside of the pooled dataset (subcutaneous injection related). The frequency is based on exposure to OPDIVO solution for injection in CA20967T and includes injection site erythema, application site pain, injection site oedema, injection site pain, application site erythema, application site rash, injection site discolouration, injection site inflammation, and injection site pruritus.

Nivolumab in combination with other therapeutic agents (see section 4.2)

Summary of the safety profile

When nivolumab is administered in combination, refer to the SmPC for the other therapeutic agents for additional information on the safety profile, prior to initiation of treatment.

Nivolumab in combination with ipilimumab (with or without chemotherapy)

In the pooled dataset of nivolumab administered in combination with ipilimumab (with or without chemotherapy) across tumour types (n = 2294) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (49%), diarrhoea (37%), rash (37%), nausea (30%), pruritus (29%), musculoskeletal pain (27%), pyrexia (24%), decreased appetite (23%), cough (22%), vomiting (19%), constipation (19%), arthralgia (19%), abdominal pain (19%), dyspnoea (18%), hypothyroidism (16%), headache (15%), upper respiratory tract infection (15%), oedema (13%), and dizziness (10%). The incidence of Grade 3-5 adverse reactions was 67% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 0.7% fatal adverse reactions

attributed to study drug. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%), pyrexia (36%), and headache (26%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate.

Nivolumab in combination with chemotherapy
In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n = 1572), with a minimum follow-up ranging from 7.4 to 20 months for gastric, GEJ or oesophageal adenocarcinoma, OSCC, or urothelial carcinoma, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥ 10%) were nausea (51%), fatigue (41%), peripheral neuropathy (34%), decreased appetite (32%), constipation (31%), diarrhoea (30%), vomiting (26%), stomatitis (19%), abdominal pain (19%), rash (19%), musculoskeletal pain (18%), pyrexia (17%), oedema (including peripheral oedema) (13%), cough (12%), and hypoalbuminaemia (10%). Incidences of Grade 3-5 adverse reactions were 72% for nivolumab in combination with chemotherapy, with 1.3% fatal adverse reactions attributed to nivolumab in combination with chemotherapy. Median duration of therapy was 6.44 months (95% CI: 5.95, 6.80) for nivolumab in combination with chemotherapy, 4.34 months (95% CI: 4.04, 4.70) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma, or OSCC, and 7.39 months (95% CI: 7.06, 8.38) for urothelial carcinoma. For resectable NSCLC, ninety-three percent (93%) of patients received 3 cycles of nivolumab in combination with chemotherapy.

Nivolumab in combination with cabozantinib

In the dataset of nivolumab intravenous formulation 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n =320), with a minimum follow-up of 16.0 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), palmar-plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysgeusia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The incidence of Grade 3-5 adverse reactions was 78%, with 0.3% fatal adverse reactions attributed to study drug.

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy) (n = 2294), nivolumab in combination with chemotherapy (n = 1572), and nivolumab in combination with cabozantinib (n = 320) are presented in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	**Combination with chemotherapy**	**Combination with cabozantinib**
Infections and infestations			
Very common	upper respiratory tract infection		upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis	upper respiratory tract infection, pneumonia[a]	pneumonia
Rare	aseptic meningitis		
Blood and lymphatic system disorders			
Very common	anaemia[b,i], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]	neutropaenia[b], anaemia[b,i], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]	anaemia[b], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]
Common	eosinophilia	febrile neutropaenia[a]	eosinophilia
Uncommon	febrile neutropaenia	eosinophilia	
Not known	haemophagocytic lymphohistiocytosis		
Immune system disorders			
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity, infusion related reaction (including cytokine release syndrome)	hypersensitivity (including anaphylactic reaction)
Uncommon			infusion related hypersensitivity reaction
Rare	sarcoidosis		
Not known	solid organ transplant rejection[f]		
Endocrine disorders			
Very common	hypothyroidism		hypothyroidism, hyperthyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus	hypothyroidism, hyperthyroidism, diabetes mellitus	adrenal insufficiency
Uncommon	diabetic ketoacidosis	adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis	hypophysitis, thyroiditis
Rare	hypoparathyroidism		

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Metabolism and nutrition disorders			
Very common	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hypoalbuminaemia, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hypoglycaemia[b], hyperglycaemia[b], weight decreased
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased	hypophosphataemia	dehydration
Uncommon	metabolic acidosis		
Rare		tumour lysis syndrome	
Not known	tumour lysis syndrome[g]		
Nervous system disorders			
Very common	headache, dizziness	peripheral neuropathy	dysgeusia, dizziness, headache
Common	peripheral neuropathy	paraesthesia, dizziness, headache	peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis		encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis), optic neuritis	Guillain-Barré syndrome, encephalitis	
Not known		myelitis (including transverse myelitis), optic neuritis	
Ear and labyrinth disorders			
Common			tinnitus
Eye disorders			
Common	blurred vision, dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt-Koyanagi-Harada syndrome		
Cardiac disorders			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia	myocarditis	myocarditis
Not known	pericardial disorders[h]		
Vascular disorders			
Very common			hypertension
Common	hypertension	thrombosis[a, j], hypertension, vasculitis	thrombosis[j]

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Respiratory, thoracic and mediastinal disorders			
Very common	cough, dyspnoea	cough	dysphonia, dyspnoea, cough
Common	pneumonitis[a], pulmonary embolism[a], pleural effusion	pneumonitis[a], dyspnoea	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders			
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation	diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis[a], pancreatitis, stomatitis, gastritis, dry mouth	colitis, dry mouth	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	duodenitis	pancreatitis	pancreatitis, small intestine perforation[a], glossodynia
Rare	intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease		
Not known		pancreatic exocrine insufficiency, coeliac disease	pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders			
Common	hepatitis		hepatitis
Uncommon		hepatitis	
Skin and subcutaneous tissue disorders			
Very common	rash[c], pruritus	rash[c], pruritus	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema,	palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, hair colour change
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders		psoriasis, urticaria
Rare	toxic epidermal necrolysis[a,d,] lichen sclerosus		
Not known			lichen sclerosus, other lichen disorders

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[e], arthralgia	musculoskeletal pain[e]	musculoskeletal pain[e], arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]		
Renal and urinary disorders			
Very common			proteinuria
Common	renal failure (including acute kidney injury)[a]	renal failure[a]	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective[g]
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain
Investigations			
Very common	increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b], hypokalaemia[b], hypercalcaemia[b], hypocalcaemia[b]	hypocalcaemia[b], increased AST[b], increased ALT[b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]	increased alkaline phosphatase[b], increased ALT[b], increased AST[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hypokalaemia[b], hypomagnesaemia[b], hyponatraemia[b], hypocalcaemia[b], hypercalcaemia[b], hypophosphataemia[b], hyperkalaemia[b], hypermagnesaemia[b], hypernatraemia[b]
Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b]	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 3 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

[c] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, nodular rash, and pemphigoid.

[d] Reported also in studies outside the pooled dataset. The frequency is based on the programme-wide exposure.
[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.
[f] Post-marketing event (also see section 4.4).
[g] Reported in clinical studies and in the post-marketing setting.
[h] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.
[i] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.
[j] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, limb venous thrombosis.

Description of selected adverse reactions

Nivolumab or nivolumab in combination with other therapeutic agents is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment generally was required in a greater proportion of patients receiving nivolumab in combination with other agents than in those receiving nivolumab monotherapy. Table 4 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 4 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

Table 4: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy, nivolumab in combination with ipilimumab (with or without chemotherapy), nivolumab in combination with chemotherapy, or nivolumab in combination with cabozantinib)

	Nivolumab monotherapy %	Nivolumab in combination with ipilimumab (with or without chemotherapy) %	Nivolumab in combination with chemotherapy %	Nivolumab in combination with cabozantinib %
Immune-related adverse reaction leading to permanent discontinuation				
Pneumonitis	1.4	2.4	1.8	2.5
Colitis	1.2	6	1.8	2.5
Hepatitis	1.1	5	0.8	4.1
Nephritis and renal dysfunction	0.3	1.2	3.3	0.6
Endocrinopathies	0.5	2.3	0.6	1.3
Skin	0.8	1.0	1.0	2.2
Hypersensitivity/Infusion reaction	0.1	0.3	1.8	0
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]				
Pneumonitis	65	59	58	56
Colitis	14	31	8	8
Hepatitis	21	36	8	23
Nephritis and renal dysfunction	22	27	7	9
Endocrinopathies	5	19	5	4.2
Skin	3.3	8	6	8
Hypersensitivity/Infusion reaction	18	16	22	0

[a] at least 40 mg daily prednisone equivalents
[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Immune-related pneumonitis
In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.3% (155/4646). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (42/4646) and 1.7% (77/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (33/4646) and <0.1% (1/4646) of patients respectively. Six patients (0.1%) had a fatal outcome. Median time to onset was 15.1 weeks (range: 0.7-85.1). Resolution occurred in 107 patients (69.0%) with a median time to resolution of 6.7 weeks (range: 0.1^{+}-109.1^{+}); $^{+}$ denotes a censored observation.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease, was 6.5% (150/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 3.2% (74/2294), 1.1% (26/2294), and 0.3% (8/2294) of patients, respectively. Four patients (0.2%) had a fatal outcome. Median time to onset was 2.7 months (range: 0.1-56.8). Resolution occurred in 124 patients (82.7%) with a median time to resolution of 6.1 weeks (range: 0.1-149.3^{+}).

In patients treated with nivolumab in combination with chemotherapy, the incidence of pneumonitis including interstitial lung disease was 4.3% (67/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (33/1572), 0.9% (14/1572), and 0.2% (3/1572), of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 25 weeks (range: 1.6-96.9). Resolution occurred in 48 patients (71.6%) with a median time to resolution of 10.4 weeks (range: 0.3^{+}-121.3^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320) of patients, respectively. Median time to onset was 26.9 weeks (range: 12.3-74.3 weeks). Resolution occurred in 14 patients (77.8%) with a median time to resolution of 7.5 weeks (range: 2.1-60.7^{+} weeks).

Immune-related colitis
In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 15.4% (716/4646). The majority of cases were Grade 1 or 2 in severity reported in 9.9% (462/4646) and 4.0% (186/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (67/4646) and <0.1% (1/4646) of patients respectively. Median time to onset was 8.3 weeks (range: 0.1-115.6). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1-124.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 27.3% (626/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 8.5% (194/2294), 6.5% (150/2294), and 0.2% (4/2294), of patients, respectively. One patient (<0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 567 patients (91%) with a median time to resolution of 2.7 weeks (range: 0.1-159.4^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of diarrhoea or colitis was 46.7%, including Grade 2 (13.6%), Grade 3 (15.8%), and Grade 4 (0.4%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of diarrhoea or colitis was 24.0% (377/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 7.3% (115/1572), 3.2% (51/1572), and 0.4% (6/1572) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 4.4 weeks (range: 0.1-93.6). Resolution occurred in 329 patients (87.7%) with a median time to resolution of 1.6 weeks (range: 0.1-212.3^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). Median time to onset was 12.9 weeks (range: 0.3-110.9 weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7^{+} weeks).

Immune-related hepatitis
In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 8.0% (371/4646). The majority of cases were Grade 1 or 2 in severity reported in 4.3% (200/4646) and 1.8% (82/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (74/4646) and 0.3% (15/4646) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-132.0). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of liver function test abnormalities was 19.3% (442/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 4.5% (104/2294), 7.5% (171/2294), and 1.1% (25/2294) of patients, respectively. Median time to onset was 2 months (range: 0.0-36.6). Resolution occurred in 388 patients (88.2%) with a median time to resolution of 5.4 weeks (range: 0.1-175.9^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of liver function test abnormalities was 30.1% including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of liver function test abnormalities was 18.6% (293/1572). Grade 2, Grade 3 and Grade 4 cases were reported in 5.6% (88/1572), 2.9% (45/1572) and < 0.1% (1/1572) of patients, respectively. Median time to onset was 7.7 weeks (range: 0.1-99.0). Resolution occurred in 231 patients (79.9%) with a median time to resolution of 7.4 weeks (range: 0.4-240.0^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. Median time to onset was 8.3 weeks (range: 0.1-107.9 weeks). Resolution occurred in 101 patients (75.9%) with a median time to resolution of 9.6 weeks (range: 0.1-89.3^{+} weeks).

Immune-related nephritis and renal dysfunction
In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.6% (121/4646). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (69/4646) and 0.7% (32/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (18/4646) and < 0.1% (2/4646) of patients, respectively. Median time to onset was 12.1 weeks (range: 0.1-79.1). Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 5.9% (135/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (50/2294), 0.9% (20/2294), and 0.5% (11/2294) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.6 months (range: 0.0-34.8). Resolution occurred in 104 patients (75.8%) with a median time to resolution of 6.1 weeks (range: 0.1-172.1^{+}).

In patients treated with nivolumab in combination with chemotherapy, the incidence of nephritis or renal dysfunction was 10.8% (170/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.1% (64/1572), 1.5% (24/1572), and 0.1% (2/1572) of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 6.9 weeks (range: 0.1-60.7). Resolution occurred in 111 patients (65.3%) with a median time to resolution of 11.6 weeks (range: 0.1-226.0^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. Median time to onset was 14.2 weeks (range: 2.1-87.1 weeks). Resolution occurred in 18 patients (58.1%) with a median time to resolution of 10.1 weeks (range: 0.6-90.9^{+} weeks).

Immune-related endocrinopathies
In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 13.0% (603/4646). The majority of cases were Grade 1 or 2 in severity reported in 6.6% (305/4646) and 6.2% (290/4646) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4646) of patients. Hypophysitis (3 Grade 1, 7 Grade 2, 9 Grade 3, and 1 Grade 4), hypopituitarism (6 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute and blood corticotrophin decreased) (2 Grade 1, 23 Grade 2, and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade 1, 3 Grade 2 and 8 Grade 3 and 2 Grade 4), were reported. Median time to onset of these endocrinopathies was 11.1 weeks (range: 0.1-126.7). Resolution occurred in 323 patients (48.7%). Median time to resolution was 48.6 weeks (range: 0.4-204.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 22.9% (526/2294). Grade 2 and Grade 3 thyroid disorders were reported in 12.2% (281/2294) and 1.0% (24/2294) of patients, respectively.
Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 2.0% (45/2294) and 1.6% (37/2294) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.7% (16/2294) and 0.5% (11/2294) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute, blood corticotrophin decreased and immune-mediated adrenal insufficiency) occurred in 2.7% (62/2294), 1.7% (39/2294) and 0.2% (4/2294) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in < 0.1% (1/2294), 0.3% (8/2294), 0.2% (5/2294), and 0.3% (6/2294) of patients, respectively. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 254 patients (39.1%). Time to resolution ranged from 0.3 to 257.1^{+} weeks.

In patients treated with nivolumab in combination with chemotherapy, the incidence of thyroid disorders was 12.7% (199/1572). Grade 2 thyroid disorder was reported in 6.2% (97/1572) patients. Grade 3 hypophysitis occurred in 0.1% (2/1572) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (3/1572) and 0.3% (4/1572) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.6% (9/1572), 0.2% (3/1572) and < 0.1% (1/1572) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus, fulminant Type 1 diabetes mellitus, and diabetic ketoacidosis (3 Grade 2, 2 Grade 3, and 1 Grade 4) were reported. Median time to onset of these endocrinopathies was 14.7 weeks (range: 1.1-124.3). Resolution occurred in 81 patients (37.2%). Time to resolution ranged from 0.4 to 233.6^{+} weeks.

In patients treated with nivolumab in combination with cabozantinib, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. Median time to onset of these endocrinopathies was 12.3 weeks (range: 2.0-89.7 weeks). Resolution occurred in 50 patients (35.2%). Time to resolution ranged from 0.9 to 132.0^{+} weeks.

Immune-related skin adverse reactions
In patients treated with nivolumab monotherapy, the incidence of rash was 30.0% (1396/4646). The majority of cases were Grade 1 in severity reported in 22.8% (1060/4646) of patients. Grade 2 and Grade 3 cases were reported in 5.9% (274/4646) and 1.3% (62/4646) of patients respectively. Median time to onset was 6.7 weeks (range: 0.1-121.1). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (0.1-192.7^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of rash was 45.2% (1038/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (312/2294), 4.4% (102/2294), and < 0.1% (2/2294) of patients, respectively. Median time to onset was 0.8 months (range: 0.0-33.8). Resolution occurred in 724 patients (70%) with a median time

to resolution of 11.3 weeks (range: 0.1-268.7[+]). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of rash was 25.6% (402/1572). Grade 2 and Grade 3 cases were reported in 6.2% (97/1572) and 2.5% (39/1572) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-97.4). Resolution occurred in 273 patients (68.1%) with a median time to resolution of 12.3 weeks (range: 0.1-258.7[+]).

In patients treated with nivolumab in combination with cabozantinib, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. Median time to onset was 6.14 weeks (range: 0.1-104.4 weeks). Resolution occurred in 137 patients (68.2%) with a median time to resolution of 18.1 weeks (range: 0.1-130.6[+] weeks).

Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4).

Infusion reactions (intravenous formulation)
In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.0% (188/4646), including 9 Grade 3 and 3 Grade 4 cases.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.8% (110/2294). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 2.0% (47/2294), 2.5% (57/2294), 0.2% (5/2294), and < 0.1% (1/2294) of patients, respectively. Among patients with MPM treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

In patients treated with nivolumab in combination with chemotherapy, the incidence of hypersensitivity/infusion reactions was 8.5% (134/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (76/1572), 1.1% (18/1572), and 0.2% (3/1572) of patients, respectively.

In patients treated with nivolumab in combination with cabozantinib, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients.

Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC
In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to nivolumab monotherapy in patients with advanced RCC. In patients with Grade ≥ 2 increased ALT or AST (n = 85): median time to onset was 10.1 weeks (range: 2.0 to 106.6 weeks), 26% received corticosteroids for median duration of 1.4 weeks (range: 0.9 to 75.3 weeks), and resolution to Grades 0-1 occurred in 91% with median time to resolution of 2.3 weeks (range: 0.4 to 108.1[+] weeks). Among the 45 patients with Grade ≥ 2 increased ALT or AST who were rechallenged with either nivolumab (n = 10) or cabozantinib (n = 10) administered as a single agent or with both (n = 25), recurrence of Grade ≥ 2 increased ALT or AST was observed in 3 patients receiving OPDIVO, 4 patients receiving cabozantinib, and 8 patients receiving both OPDIVO and cabozantinib.

Laboratory abnormalities
In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.4% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.7% for leucopoenia, 8.7% for lymphopaenia, 0.9% for neutropaenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.3% for increased ALT, 0.8% for increased total bilirubin, 0.7% for increased creatinine, 2.0% for hyperglycaemia, 0.7% for hypoglycaemia, 3.8% for increased amylase, 6.9% for increased lipase, 4.7% for hyponatraemia, 1.6% for hyperkalaemia, 1.3% for hypokalaemia, 1.1% for hypercalcaemia, 0.6% for

hypermagnesaemia, 0.4% for hypomagnesaemia, 0.6% for hypocalcaemia, 0.6% for hypoalbuminaemia, and <0.1% for hypernatraemia.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.8% for anaemia, 1.4% for thrombocytopaenia, 2.1% for leucopoenia, 7.0% for lymphopaenia, 3.2% for neutropaenia, 2.8% for increased alkaline phosphatase, 7.0% for increased AST, 8.1% for increased ALT, 1.3% for increased total bilirubin, 1.7% for increased creatinine, 5.8% for hyperglycaemia, 0.7% for hypoglycaemia, 8.2% for increased amylase, 16.3% for increased lipase, 0.7% for hypocalcaemia, 0.2% for hypernatraemia, 0.9% for hypercalcaemia, 1.9% for hyperkalaemia, 0.5% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.2% for hypokalaemia, and 9.2% for hyponatraemia.

Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, a higher proportion of patients experienced a worsening from baseline to Grade 3 or 4 increased ALT (15.3%).

In patients treated with nivolumab in combination with chemotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 15.8% for anaemia, 6.9% for thrombocytopaenia, 12.2% leukopaenia, 14.6% for lymphopaenia, 27.6% neutropaenia, 2.4% for increased alkaline phosphatase, 3.4% for increased AST, 2.6% for increased ALT, 2.0% for increased bilirubin, 1.4% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.5% for hypernatraemia, 8.8% for hyponatraemia, 1.9% for hyperkalaemia, 5.6% for hypokalaemia, 0.8% for hypercalcaemia, 1.9% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.5% for hyperglycaemia, and 0.7% for hypoglycaemia.

In patients treated with nivolumab in combination with cabozantinib, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.5% for anaemia (all Grade 3), 0.3% for thrombocytopaenia, 0.3% for leucopoenia, 7.5% for lymphopaenia, 3.5% for neutropaenia, 3.2% for increased alkaline phosphatase, 8.2% for increased AST, 10.1% for increased ALT, 1.3% for increased total bilirubin, 1.3% for increased creatinine, 11.9% for increased amylase, 15.6% for increased lipase, 3.5% for hyperglycaemia, 0.8% for hypoglycaemia, 2.2% for hypocalcaemia, 0.3% for hypercalcaemia, 5.4% for hyperkalaemia, 4.2% for hypermagnesaemia, 1.9% for hypomagnesaemia 3.2% for hypokalaemia, 12.3% for hyponatraemia, and 21.2% for hypophosphataemia.

Immunogenicity

Subcutaneous formulation
Of the 202 patients who were treated with nivolumab solution for injection and evaluable for the presence of anti-nivolumab antibodies, approximately 23% (46/202) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 1% (2/202) had neutralizing antibodies against nivolumab. The incidence of treatment-emergent anti-recombinant human hyaluronidase PH20 (anti-rHuPH20) antibodies in patients treated with nivolumab solution for injection was 8.8% (19/215).

Intravenous formulation
Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 patients (9.3%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.6%) testing positive for neutralising antibodies.

Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 7.5% tested positive for treatment emergent anti-product-antibodies with 0.5% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-nivolumab antibodies or neutralising antibodies against nivolumab, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralising antibodies was 2.6%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralising antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and the neutralising antibodies was 1.6%.

Although the clearance of nivolumab was increased by 20% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination.

Elderly

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see section 5.1).

For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1).

Hepatic or renal impairment

In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/ death ligand 1) inhibitors. ATC code: L01FF01.

OPDIVO solution for injection contains the active substance nivolumab, which provides the therapeutic effect of this medicinal product, and recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously.

Mechanism of action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

Clinical efficacy and safety

Subcutaneous formulation
Results from a simulation-based pharmacokinetic bridging analyses showed that across all solid tumour types evaluated, subcutaneous nivolumab dosing regimens (600 mg every 2 weeks and 1200 mg every 4 weeks) produced exposures that were noninferior (geometric mean ratio > 1) to those for the approved intravenous nivolumab dosing regimens (240 mg every 2 weeks and 480 mg every 4 weeks). Geometric mean exposures were also below those for intravenous nivolumab 10 mg/kg Q2W, a regimen shown to be safe in clinical studies.

The subcutaneous nivolumab clinical safety profile was comparable to intravenous nivolumab.

Melanoma

Treatment of advanced melanoma

Intravenous formulation

Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an ECOG performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

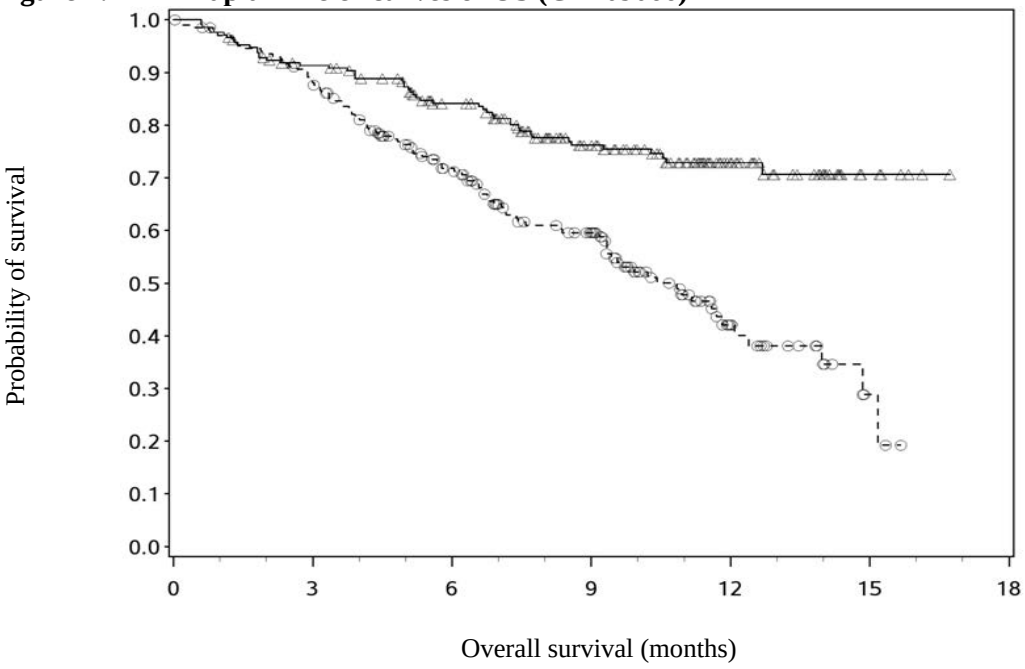
A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1 000 mg/m^2

every 3 weeks. Randomisation was stratified by tumour PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse events with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and objective response rate (ORR).

Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma (≥ 5% tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

The Kaplan-Meier curves for OS are shown in Figure 1.

Figure 1: Kaplan-Meier curves of OS (CA209066)



Number of subjects at risk

Nivolumab						
210	185	150	105	45	8	0
Dacarbazine						
208	177	123	82	22	3	0

----△---- Nivolumab (events: 50/210), median and 95% CI: N.A.
- - -❍- - - Dacarbazine (events: 96/208), median and 95% CI: 10.84 (9.33, 12.09)

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%).

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Efficacy results are shown in Table 5.

Table 5: Efficacy results (CA209066)

	nivolumab (n = 210)		dacarbazine (n = 208)
Overall survival			
Events	50 (23.8%)		96 (46.2%)
Hazard ratio		0.42	
99.79% CI		(0.25, 0.73)	
95% CI		(0.30, 0.60)	
p-value		< 0.0001	
Median (95% CI)	Not reached		10.8 (9.33, 12.09)
Rate (95% CI)			
At 6 months	84.1 (78.3, 88.5)		71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)		42.1 (33.0, 50.9)
Progression-free survival			
Events	108 (51.4%)		163 (78.4%)
Hazard ratio		0.43	
95% CI		(0.34, 0.56)	
p-value		< 0.0001	
Median (95% CI)	5.1 (3.48, 10.81)		2.2 (2.10, 2.40)
Rate (95% CI)			
At 6 months	48.0 (40.8, 54.9)		18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)		NA
Objective response	84 (40.0%)		29 (13.9%)
(95% CI)	(33.3, 47.0)		(9.5, 19.4)
Odds ratio (95% CI)		4.06 (2.52, 6.54)	
p-value		< 0.0001	
Complete response (CR)	16 (7.6%)		2 (1.0%)
Partial response (PR)	68 (32.4%)		27 (13.0%)
Stable disease (SD)	35 (16.7%)		46 (22.1%)
Median duration of response			
Months (range)	Not reached	(0^+-12.5^+)	6.0 (1.1-10.0^+)
Median time to response			
Months (range)	2.1 (1.2-7.6)		2.1 (1.8-3.6)

"+" denotes a censored observation.

Intravenous formulation

Randomised phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, open-label study (CA209037). The

study included adult patients who had progressed on or after ipilimumab and if BRAF V600 mutation positive had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma, active brain or leptomeningeal metastases or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and tumour PD-L1 status and best response to prior ipilimumab.

The co-primary efficacy outcome measures were confirmed ORR in the first 120 patients treated with nivolumab, as measured by independent radiology review committee (IRRC) using RECIST, version 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and > 2 for 21% of patients. Twenty-two percent of patients had tumours that tested BRAF mutation positive and 50% of patients had tumours that were considered PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. Efficacy results are presented in Table 6.

Table 6: Best overall response, time and duration of response (CA209037)

	nivolumab (n = 120)	**chemotherapy (n = 47)**
Confirmed objective response (IRRC)	38 (31.7%)	5 (10.6%)
(95% CI)	(23.5, 40.8)	(3.5, 23.1)
Complete response (CR)	4 (3.3%)	0
Partial response (PR)	34 (28.3%)	5 (10.6%)
Stable disease (SD)	28 (23.3%)	16 (34.0%)
Median duration of response		
Months (range)	Not reached	3.6 (Not available)
Median time to response		
Months (range)	2.1 (1.6-7.4)	3.5 (2.1-6.1)

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Updated analysis (24-month follow-up)
Among all randomised patients, the ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median durations of response were 31.9 months

(range: 1.4^{+}-31.9) and 12.8 months (range: 1.3^{+}-13.6^{+}), respectively. The PFS HR for nivolumab vs. chemotherapy was 1.03 (95% CI: 0.78, 1.36). The ORR and PFS were assessed by IRRC per RECIST version 1.1.

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm.

Efficacy by BRAF status: Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. The ORRs in the BRAF mutation-positive subgroup were 17% (95% CI: 8.4, 29.0) for nivolumab and 11% (95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (95% CI: 24.0, 36.7) and 9% (95% CI: 4.6, 16.7), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 1.58 (95% CI: 0.87, 2.87) for BRAF mutation-positive patients and 0.82 (95% CI: 0.60, 1.12) for BRAF wild-type patients. The OS HRs for nivolumab vs. chemotherapy were 1.32 (95% CI: 0.75, 2.32) for BRAF mutation-positive patients and 0.83 (95% CI: 0.62, 1.11) for BRAF wild-type patients.

Efficacy by tumour PD-L1 expression: Objective responses to nivolumab were observed regardless of tumour PD-L1 expression. However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated.

In patients with tumour PD-L1 expression ≥ 1%, ORR was 33.5% for nivolumab (n = 179; 95% CI: 26.7, 40.9) and 13.5% for chemotherapy (n = 74; 95% CI: 6.7, 23.5). In patients with tumour PD-L1 expression <1%, ORR per IRRC was 13.0% (n = 69; 95% CI: 6.1, 23.3) and 12.0% (n = 25; 95% CI: 2.5, 31.2), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 0.76 (95% CI: 0.54, 1.07) in patients with tumour PD-L1 expression ≥ 1% and 1.92 (95% CI: 1.05, 3.5) in patients with tumour PD-L1 expression < 1%.

The OS HRs for nivolumab vs. chemotherapy were 0.69 (95% CI: 0.49, 0.96) in patients with tumour PD-L1 expression ≥ 1% and 1.52 (95% CI: 0.89, 2.57) in patients with tumour PD-L1 expression < 1%.

These subgroup analyses should be interpreted with caution given the small size of the subgroups and lack of statistically significant difference in OS in the all randomised population.

Intravenous formulation

Open-label phase 1 dose-escalation study (MDX1106-03)
The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma. Of the 306 previously treated patients enrolled in the study, 107 had melanoma and received nivolumab at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg for a maximum of 2 years. In this patient population, objective response was reported in 33 patients (31%) with a median duration of response of 22.9 months (95% CI: 17.0, NR). The median PFS was 3.7 months (95% CI: 1.9, 9.3). The median OS was 17.3 months (95% CI: 12.5, 37.8), and the estimated OS rates were 42% (95% CI: 32, 51) at 3 years, 35% (95% CI: 26, 44) at 4 years, and 34% (95% CI: 25, 43) at 5 years (minimum follow-up of 45 months).

Intravenous formulation

Single-arm phase 2 study (CA209172)
Study CA209172 was a single-arm, open label study of nivolumab monotherapy in patients with stage III (unresectable) or stage IV metastatic melanoma after prior treatment containing an anti-CTLA-4 monoclonal antibody. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 1 008 treated patients, 103 (10%) had ocular/uveal melanoma, 66 (7%) had an ECOG performance score of 2, 165 (16%) had asymptomatic treated and untreated CNS metastases, 13 (1.3%) had treated leptomeningeal metastases, 25 (2%) had autoimmune disease, and 84 (8%) had Grade 3-4 immune-related AEs with prior anti-CTLA-4 therapy. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed response rates at week 12 are presented in Table 7 below.

Table 7: Response rate at week 12 - all response evaluable patients and by subgroup (CA209172)

	Total	Ocular/ Uveal melanoma	ECOG PS 2	CNS metastasis	Autoimmune disease	Grade 3-4 irAEs with anti-CTLA-4
N (%)[a]	161/588 (27.4)	4/61 (6.6)	4/20 (20.0)	20/73 (27.4)	3/16 (18.8)	13/46 (28.3)

[a] Responses were assessed per RECIST 1.1 for 588/1008 (58.3%) of patients who continued treatment through week 12 and had a follow-up scan at week 12.

Intravenous formulation

Randomised phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy vs. ipilimumab as monotherapy (CA209067)
The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg or nivolumab 3 mg/kg vs. ipilimumab 3 mg/kg monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209067). The differences between the two nivolumab-containing groups were evaluated descriptively. The study included adult patients with confirmed unresectable Stage III or Stage IV melanoma. Patients were to have ECOG performance status score of 0 or 1. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled. Prior adjuvant or neoadjuvant therapy was allowed if it was completed at least 6 weeks prior to randomisation. Patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases were excluded from the study.

A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomisation was stratified by PD-L1 expression (≥ 5% vs. < 5% tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted 12 weeks after randomisation then every 6 weeks for the first year, and every 12 weeks thereafter. The primary outcome measures were progression-free survival and OS. ORR and the duration of response were also assessed.

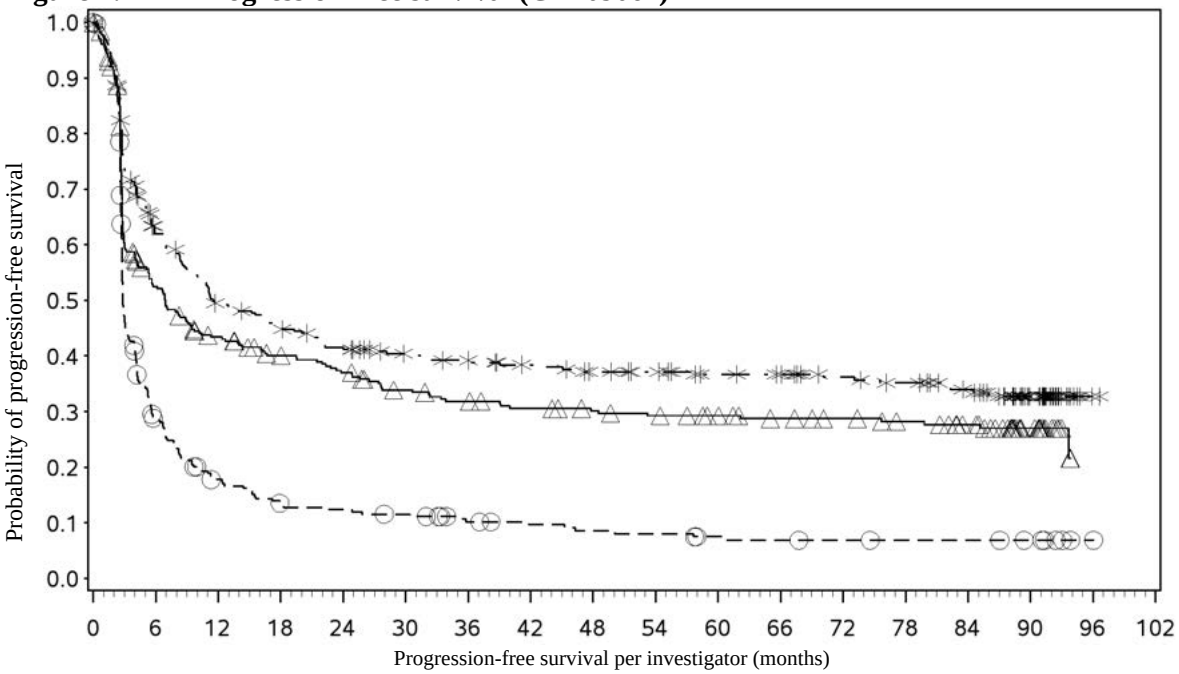
Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18 to 90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy.

Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1 ≥ 5% tumour cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the three treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

At primary analysis (minimum follow-up 9 months) the median PFS was 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR = 0.57, 99.5% CI: 0.43, 0.76; p < 0.0001). The median PFS was 11.5 months in the nivolumab in combination with ipilimumab group, as compared with 2.9 months in the ipilimumab group (HR = 0.42, 99.5% CI: 0.31, 0.57; p < 0.0001).

PFS results from descriptive analysis (with minimum follow up of 90 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

Figure 2: Progression-free survival (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab																	
314	175	138	126	112	103	99	93	87	84	78	76	70	66	57	33	1	-
Nivolumab																	
316	151	120	106	97	84	78	73	69	66	62	57	54	50	44	21	0	-
Ipilimumab																	
315	78	46	34	31	28	21	18	16	15	12	11	10	9	9	7	1	-

- - -✳- - - Nivolumab+ipilimumab (events: 189/314), median and 95% CI: 11.50 (8.90, 20.04).
PFS rate at 12 months and 95% CI: 49% (44, 55), PFS rate at 60 months and 95% CI: 36% (32, 42), PFS rate at 90 months and 95% CI: 33% (27, 39)

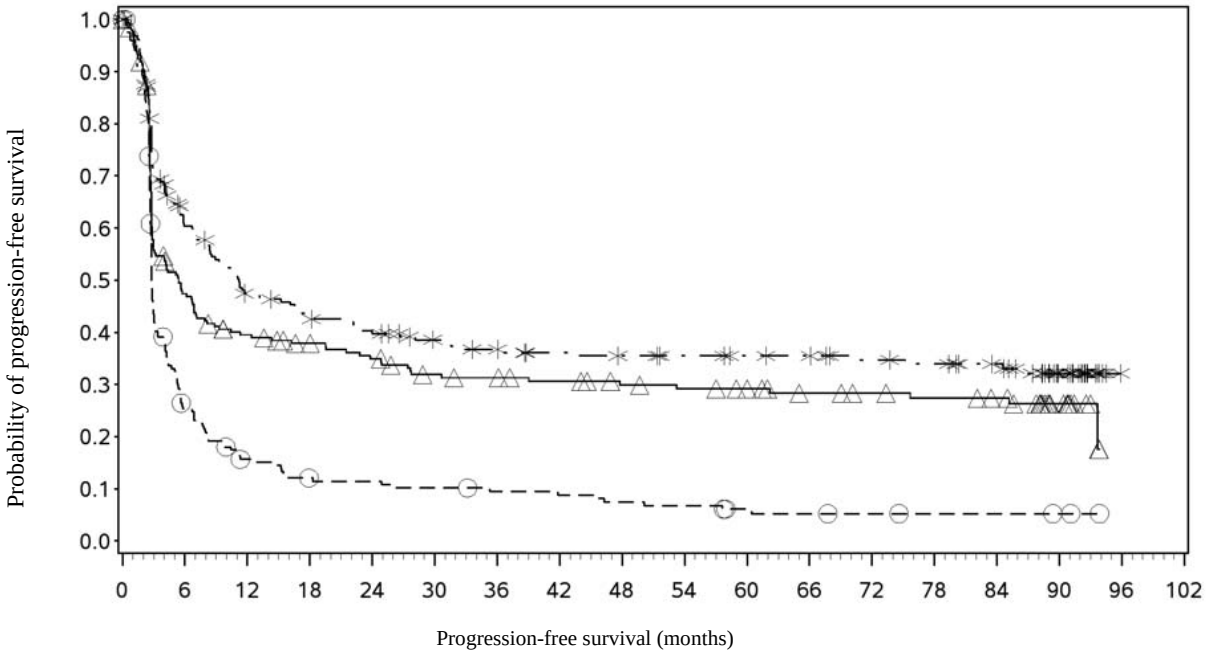
----△---- Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)

- - -❍- - - Ipilimumab (events: 261/315), median and 95% CI: 2.86 (2.79, 3.09).
PFS rate at 12 months and 95% CI: 18% (14, 23), PFS rate at 60 months and 95% CI: 8% (5, 12), PFS rate at 90 months and 95% CI: 7% (4, 11)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.35, 0.51)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.53 (0.44, 0.64)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.79 (0.65, 0.97)

Figure 3: Progression-free survival by PD-L1 expression: 5% cut off (CA209067)

PD-L1 expression < 5%



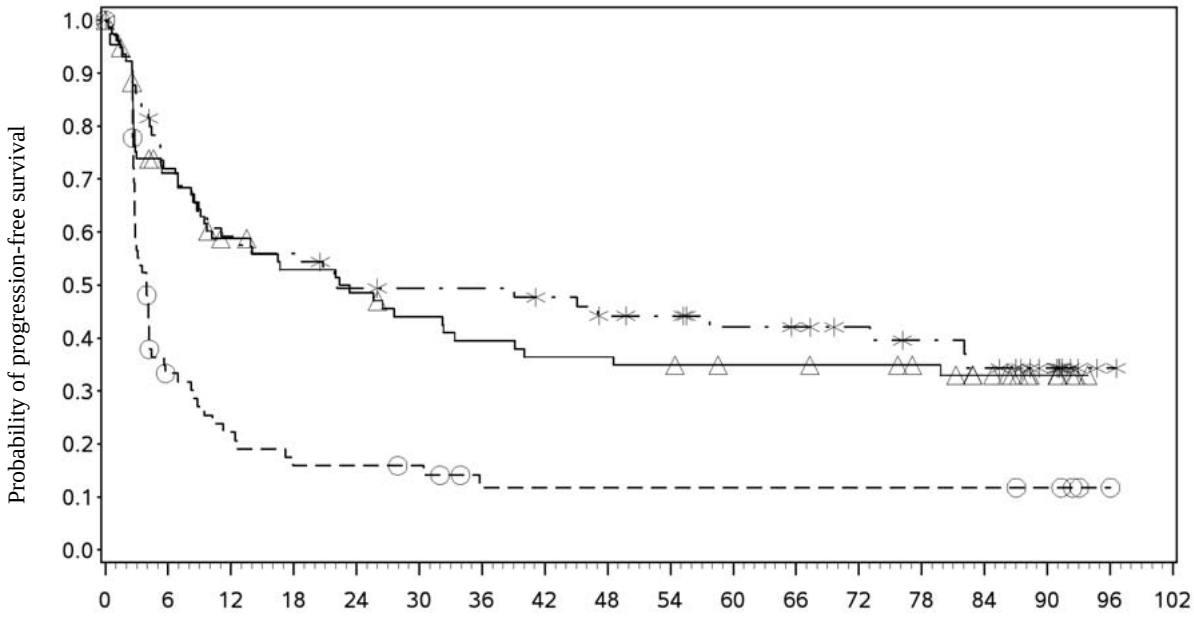
Number of subjects at risk

Nivolumab + ipilimumab																	
210	113	87	78	71	64	60	56	54	52	50	49	45	43	39	22	0	-
Nivolumab																	
208	91	73	66	60	51	49	46	42	40	38	33	31	29	27	12	0	-
Ipilimumab																	
202	45	26	19	18	16	14	13	11	10	7	6	5	4	4	3	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 127/210), median and 95% CI: 11.17 (7.98, 17.51)
----△---- Nivolumab (events: 139/208), median and 95% CI: 5.39 (2.96, 7.13)
- - -❍- - - Ipilimumab (events: 171/202), median and 95% CI: 2.79 (2.76, 3.02)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.33, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.54 (0.43, 0.68)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.77 (0.61, 0.98)

PD-L1 expression ≥ 5%



Number of subjects at risk

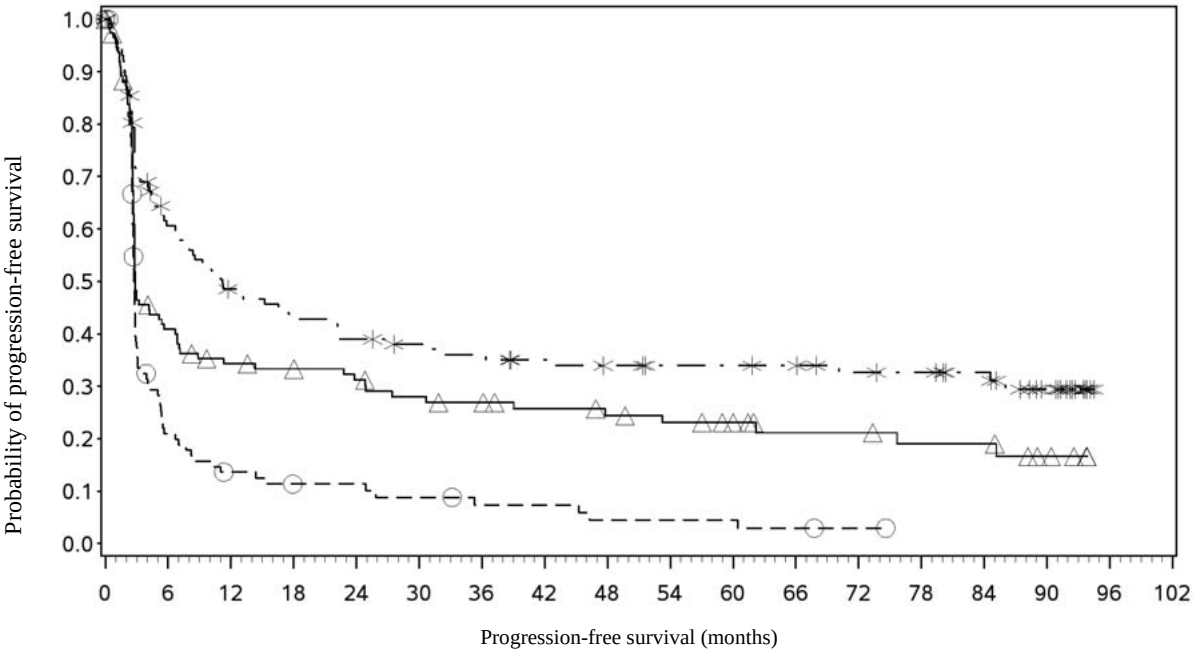
Nivolumab + ipilimumab																	
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1	-
Nivolumab																	
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0	-
Ipilimumab																	
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1	-

- - -✳- - - Nivolumab+ipilimumab (events: 36/68), median and 95% CI: 22.11 (9.72, 82.07)
----△---- Nivolumab (events: 48/80), median and 95% CI: 22.34 (9.46, 39.13)
- - -❍- - - Ipilimumab (events: 60/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.38 (0.25, 0.58)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.43 (0.29, 0.64)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.89 (0.58, 1.35)

Figure 4: Progression-free survival by PD-L1 expression: 1% cut off (CA209067)

PD-L1 expression < 1%



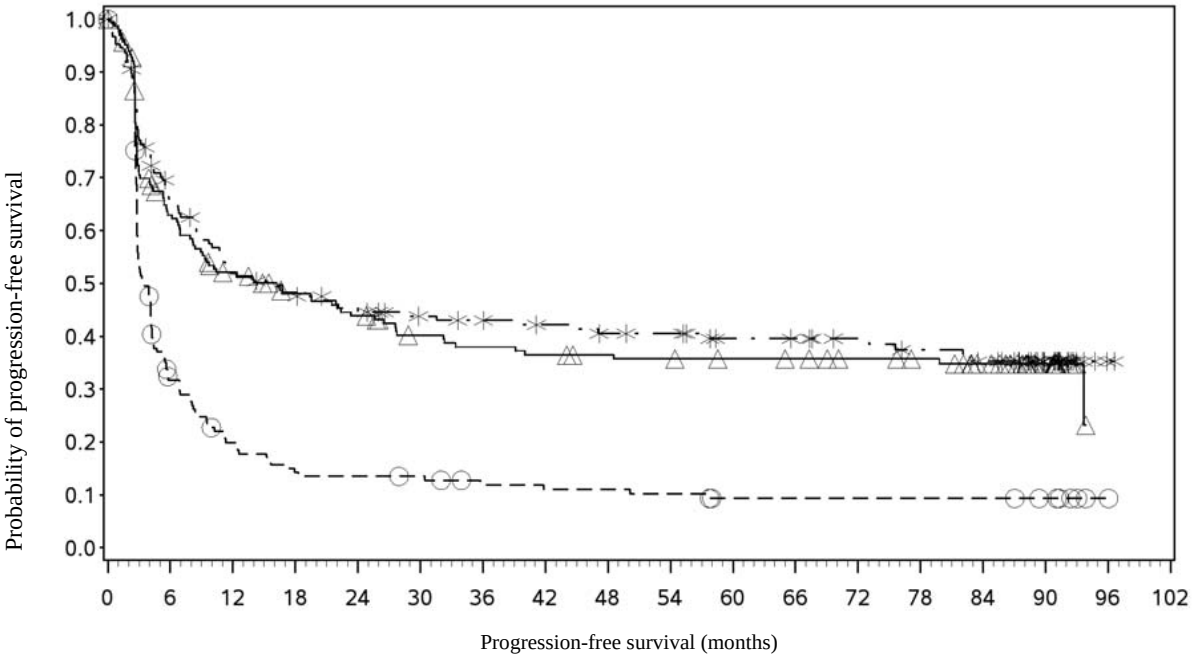
Number of subjects at risk

Nivolumab + ipilimumab																	
123	65	51	46	41	38	36	33	31	29	29	28	25	24	21	13	0	-
Nivolumab																	
117	44	35	33	30	26	24	21	19	17	15	11	11	9	9	5	0	-
Ipilimumab																	
113	20	12	9	9	7	5	5	3	3	3	2	1	0	0	0	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 76/123), median and 95% CI: 11.17 (6.93, 22.18)
----△---- Nivolumab (events: 85/117), median and 95% CI: 2.83 (2.76, 5.62)
- - -❍- - - Ipilimumab (events: 94/113), median and 95% CI: 2.73 (2.66, 2.83)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.39 (0.28, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.59 (0.44, 0.79)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.66 (0.48, 0.90)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab + ipilimumab																	
155	93	73	67	60	55	53	50	47	46	41	40	37	34	31	17	1	-
Nivolumab																	
171	99	79	69	63	54	51	49	47	46	44	43	40	38	32	14	0	-
Ipilimumab																	
164	46	28	20	19	18	14	13	13	12	9	9	9	9	9	7	1	-

- - -✳- - - Nivolumab+ipilimumab (events: 90/155), median and 95% CI: 16.13 (8.90, 45.08)
----△---- Nivolumab (events: 102/171), median and 95% CI: 16.20 (8.11, 27.60)
- - -❍- - - Ipilimumab (events: 137/164), median and 95% CI: 3.48 (2.83, 4.17)

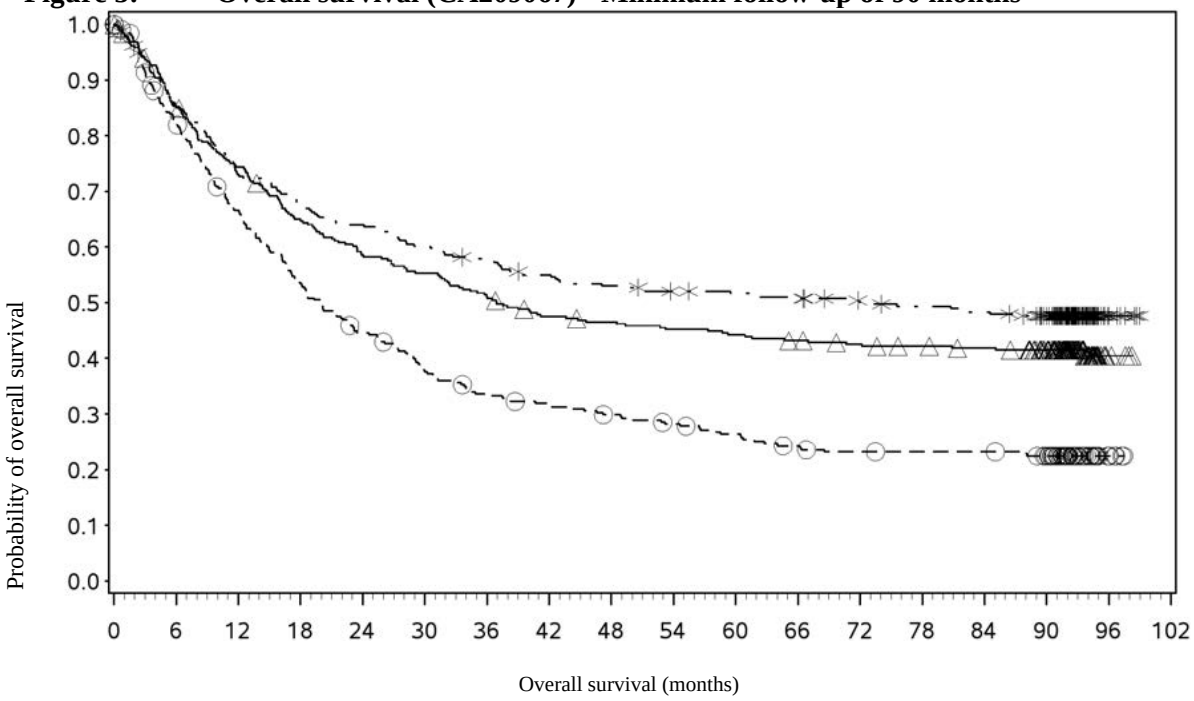
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

The final (primary) OS analysis occurred when all patients had a minimum follow-up of 28 months. At 28 months, median OS was not reached in the nivolumab group as compared with 19.98 months in the ipilimumab group (HR = 0.63, 98% CI: 0.48, 0.81; p-value: < 0.0001). Median OS was not reached in the nivolumab in combination with ipilimumab group as compared with the ipilimumab group (HR = 0.55, 98% CI: 0.42, 0.72; p-value: < 0.0001).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 90 months show outcomes consistent with the original primary analysis. OS results from this follow-up analysis are shown in Figure 5 (all randomised), Figures 6 and 7 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 36.0%, 49.1%, and 66.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 19.1%, 34.2%, and 48.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 5: Overall survival (CA209067) - Minimum follow-up of 90 months



Number of subjects at risk

Nivolumab+ipilimumab																	
314	265	227	210	199	187	179	169	163	158	156	153	147	144	141	129	7	-
Nivolumab																	
316	266	231	201	181	171	158	145	141	137	134	130	126	123	120	107	4	-
Ipilimumab																	
315	253	203	163	135	113	100	94	87	81	75	68	64	63	63	57	5	-

- - -✳- - - Nivolumab+ipilimumab (events: 162/314), median and 95% CI: 72.08 (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), 36 months: 58% (52, 63), 60 months: 52% (46, 57), and 90 months: 48% (42, 53)

----△---- Nivolumab (events: 182/316), median and 95% CI: 36.93 months (28.25, 58.71)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57), 60 months: 44% (39, 50), and 90 months: 42% (36, 47)

- - -❍- - - Ipilimumab (events: 235/315), median and 95% CI: 19.94 months (16.85, 24.61)
OS rate and 95% CI at 12 months: 67% (61, 72), 24 months: 45% (39, 50), 36 months: 34% (29, 39), 60 months: 26% (22, 31), and 90 months: 22% (18, 27)

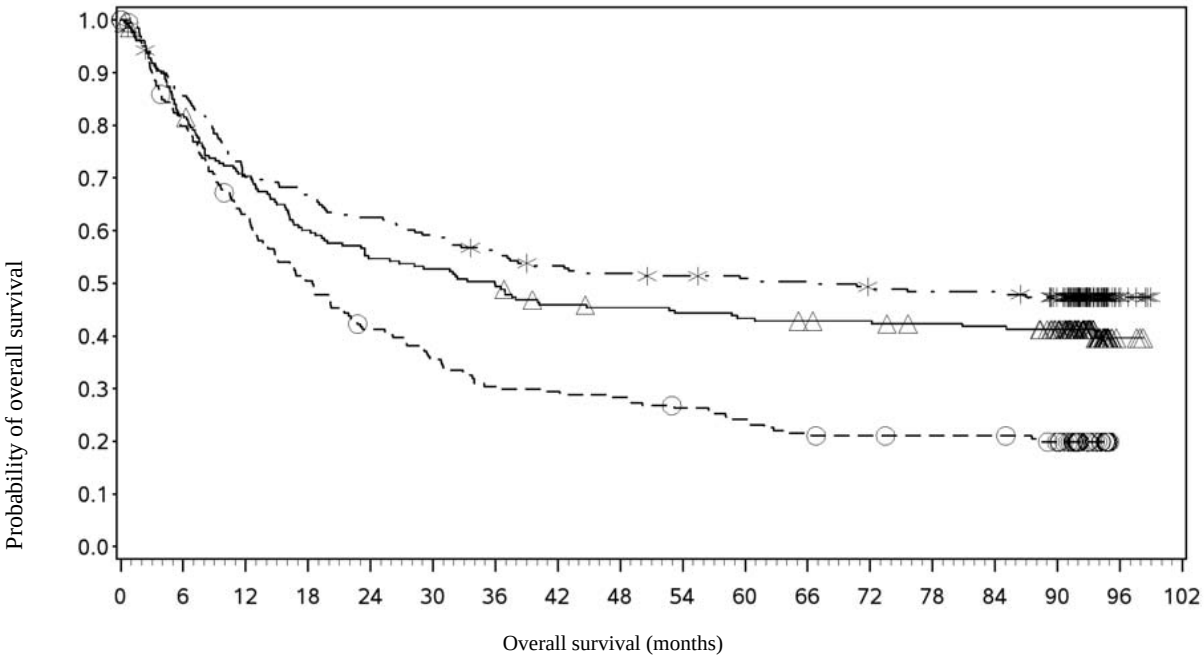
Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65)

Nivolumab vs ipilimumab - HR (95% CI): 0.63 (0.52, 0.77)

Nivolumab+ipilimumab vs nivolumab - HR (95% CI): 0.84 (0.68, 1.04)

Figure 6: Overall survival by PD-L1 expression: 5% cut off (CA209067) - Minimum follow-up of 90 months

PD-L1 expression < 5%



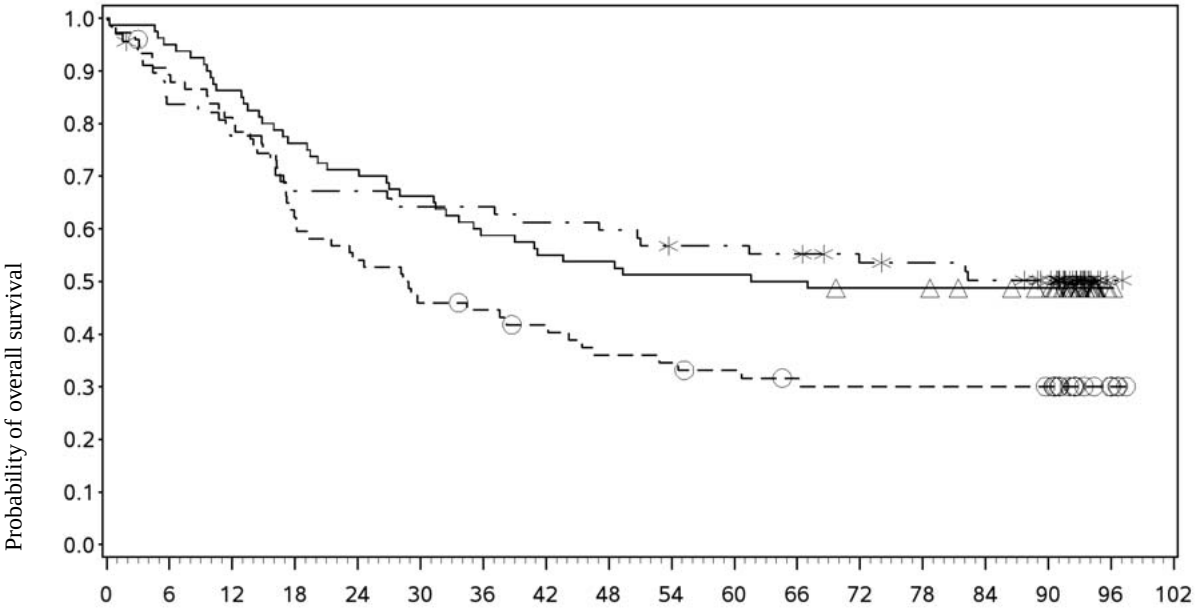
Number of subjects at risk

Nivolumab+ipilimumab																	
210	178	146	139	130	123	116	109	106	104	102	100	98	96	96	88	6	-
Nivolumab																	
208	169	144	123	112	108	102	92	90	88	86	84	83	80	79	70	3	-
Ipilimumab																	
202	158	124	99	80	69	59	57	55	50	46	41	39	38	38	33	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 109/210), median and 95% CI: 65.94 (32.72, N.A.)
----△---- Nivolumab (events: 121/208), median and 95% CI: 35.94 months (23.06, 60.91)
- - -❍- - - Ipilimumab (events: 157/202), median and 95% CI: 18.40 months (13.70, 22.51)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.51 (0.40, 0.66)
Nivolumab vs. ipilimumab - HR (95% CI): 0.62 (0.49, 0.79)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.83 (0.64, 1.07)

PD-L1 expression ≥ 5%



Number of subjects at risk

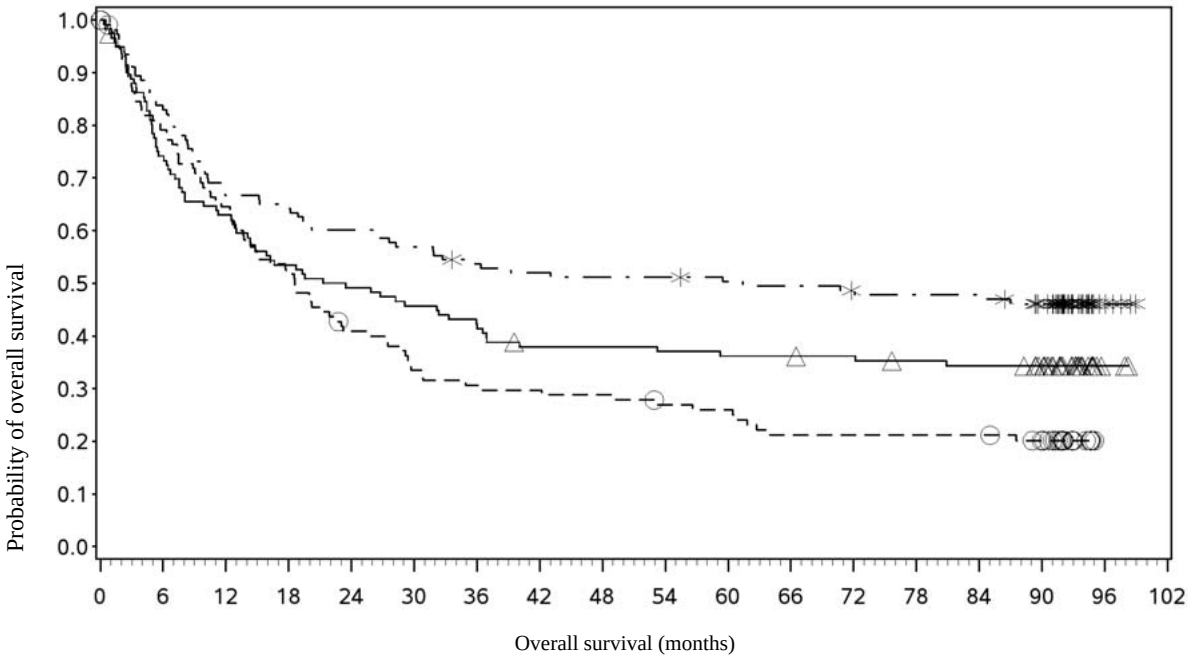
Nivolumab+ipilimumab																	
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1	-
Nivolumab																	
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1	-
Ipilimumab																	
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4	-

- - -✳- - - Nivolumab+ipilimumab (events: 33/68), median and 95% CI: N.A. (39.06, N.A.)
----△---- Nivolumab (events: 41/80), median and 95% CI: 64.28 months (33.64, N.A.)
- - -❍- - - Ipilimumab (events: 51/75), median and 95% CI: 28.88 months (18.10, 44.16)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.61 (0.39, 0.94)
Nivolumab vs. ipilimumab - HR (95% CI): 0.61 (0.41, 0.93)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.99 (0.63, 1.57)

Figure 7: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 90 months

PD-L1 expression < 1%



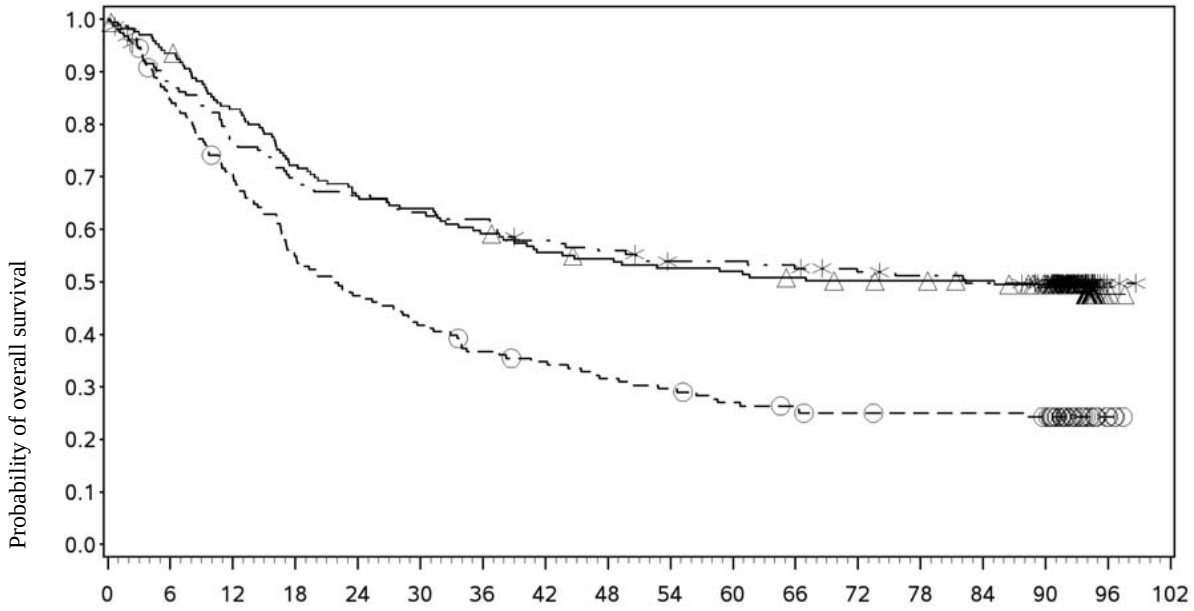
Number of subjects at risk

Nivolumab+ipilimumab																	
123	102	82	79	74	70	65	63	62	62	62	60	59	57	56	50	5	-
Nivolumab																	
117	86	73	62	57	53	49	43	43	42	41	41	40	38	37	33	2	-
Ipilimumab																	
113	87	71	57	44	36	33	32	31	28	27	22	22	22	22	18	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 66/123), median and 95% CI: 61.44 (26.45, N.A.)
----△---- Nivolumab (events: 76/117), median and 95% CI: 23.46 months (13.01, 36.53)
- - -❍- - - Ipilimumab (events: 87/113), median and 95% CI: 18.56 months (13.67, 23.20)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.55 (0.40, 0.76)
Nivolumab vs. ipilimumab - HR (95% CI): 0.77 (0.57, 1.05)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.71 (0.51, 0.99)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab+ipilimumab																	
155	132	116	105	101	96	94	87	84	79	79	77	74	72	70	65	2	-
Nivolumab																	
171	159	140	122	112	108	100	93	90	87	86	83	81	80	78	70	2	-
Ipilimumab																	
164	137	113	88	76	67	58	54	49	46	41	39	36	35	35	33	4	-

- - -✳- - - Nivolumab+ipilimumab (events: 76/155), median and 95% CI: 82.30 (39.06, N.A.)
----△---- Nivolumab (events: 86/171), median and 95% CI: 85.09 months (39.00, N.A.)
- - -❍- - - Ipilimumab (events: 121/164), median and 95% CI: 21.49 months (16.85, 29.08)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.70)
Nivolumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.69)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 1.01 (0.74, 1.37)

Minimum follow-up for the analysis of ORR was 90 months. Responses are summarised in Table 8.

Table 8: Objective response (CA209067)

	nivolumab + ipilimumab (n = 314)	**nivolumab (n = 316)**	**ipilimumab (n = 315)**
Objective response	183 (58%)	142 (45%)	60 (19%)
(95% CI)	(52.6, 63.8)	(39.4, 50.6)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.35	3.5	
(95% CI)	(4.38, 9.22)	(2.49, 5.16)	
Complete response (CR)	71(23%)	59 (19%)	19 (6%)
Partial response (PR)	112 (36%)	83 (26%)	41 (13%)
Stable disease (SD)	38 (12%)	29 (9%)	69 (22%)
Duration of response			
Median (range), months	N.A. (69.1-N.A.)	90.8 (45.7-N.A.)	19.3 (8.8-47.4)
Proportion ≥ 12 months in duration	68%	73%	44%
Proportion ≥ 24 months in duration	58%	63%	30%
ORR (95% CI) by tumour PD-L1 expression			
< 5%	56% (48.7, 62.5) n = 210	43% (36, 49.8) n = 208	18% (12.8, 23.8) n = 202
≥ 5%	72% (59.9, 82.3) n = 68	59% (47.2, 69.6) n = 80	21% (12.7, 32.3) n = 75
< 1%	54% (44.4, 62.7) n = 123	36% (27.2, 45.3) n = 117	18% (11.2, 26.0) n = 113
≥ 1%	65% (56.4, 72) n = 155	55% (47.2, 62.6) n = 171	20% (13.7, 26.4) n = 164

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab alone. The observed PFS results at 18 months of follow-up and ORR and OS results at 28 months of follow-up were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level. This observation was maintained with the OS results with a minimum follow-up of 90 months.

Among 131 patients who discontinued the combination due to adverse reaction after 28 months of follow-up, the ORR was 71% (93/131) with 20% (26/131) achieving a complete response and median OS was not reached.

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 8) after 90 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 90 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥ 5% were 78.19 months (range: 18.07-N.A.) in the combination arm,77.21 months (range: 26.25-N.A.) in the nivolumab monotherapy arm and 31.28 months (range: 6.08-N.A.) in the ipilimumab arm. At tumour PD-L1 expression < 5%, median durations of response were not reached (range: 61.93-N.A.) in the combination arm, were 90.84 months (range: 50.43-N.A.) in the nivolumab monotherapy arm and 19.25 months (range: 5.32-47.44) in the ipilimumab monotherapy arm.

No clear cut off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS and OS. Results from exploratory multivariate analyses

identified patient and tumour characteristics (ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status, and gender) which might contribute to the survival outcome.

Efficacy by BRAF status:
After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.7 months (95% CI: 7.0, 19.32), while those in the nivolumab monotherapy arm had a median PFS of 5.62 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had a median PFS of 3.09 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively.

After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215).

After 90 months of follow-up, in BRAF [V600] mutation-positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab monotherapy arm. Median OS for BRAF [V600] mutation-positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild-type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.66 (95% CI: 0.44, 0.98) for BRAF[V600] mutation-positive patients and 0.95 (95% CI: 0.74, 1.22) for BRAF wild-type patients.

Intravenous formulation

Randomised phase 2 study of nivolumab in combination with ipilimumab and ipilimumab (CA209069)
Study CA209069 was a randomised, Phase 2, double-blind study comparing the combination of nivolumab and ipilimumab with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma with similar inclusion criteria to study CA209067 and the primary analysis in patients with BRAF wild-type melanoma (77% of patients). Investigator assessed ORR was 61% (95% CI: 48.9, 72.4) in the combination arm (n = 72) versus 11% (95% CI: 3.0, 25.4) for the ipilimumab arm (n = 37). The estimated 2 and 3 year OS rates were 68% (95% CI: 56, 78) and 61% (95% CI: 49, 71), respectively, for the combination (n = 73) and 53% (95% CI: 36, 68) and 44% (95% CI: 28, 60), respectively, for ipilimumab (n = 37).

Adjuvant treatment of melanoma

Intravenous formulation

Randomised phase 3 study of nivolumab vs. placebo (CA20976K)
The safety and efficacy of nivolumab 480 mg monotherapy for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA20976K). The study included patients with an ECOG performance status score of 0 or 1 who had Stage IIB or IIC American Joint Committee on Cancer (AJCC), 8th edition, histologically confirmed melanoma that had been completely surgically resected. Enrolment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node biopsy within 12 weeks prior to randomisation. Patients were enrolled regardless of their tumour PD-L1 status. The study excluded patients with ocular/uveal or mucosal melanoma, active autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery.

A total of 790 patients were randomised (2:1) to receive either nivolumab (n = 526) administered intravenously over 30 minutes at 480 mg every 4 weeks or placebo (n = 264) for up to 1 year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by AJCC 8th edition T-category (T3b vs. T4a vs. T4b). Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 3 years to 5 years. The primary efficacy outcome measure was recurrence-free survival (RFS). RFS, assessed by the investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first. The secondary outcome measures included OS and distant metastasis-free survival (DMFS).

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 19-92), 61% were men, and 98% were white. Baseline ECOG performance status score was 0 (94%) or 1 (6%). Sixty percent had stage IIB and 40% had stage IIC.

At a primary pre-specified interim analysis (minimum follow-up 7.8 months) a statistically significant improvement in RFS was demonstrated with nivolumab compared to placebo with a HR of 0.42 (95% CI: 0.30, 0.59; $p < 0.0001$). At an updated descriptive RFS analysis (minimum follow-up of 15.6 months), nivolumab continued to demonstrate an RFS improvement with a HR of 0.53 (95% CI: 0.40, 0.71). OS was not mature. Results reported from the analyses with minimum follow-up of 15.6 months are summarised in Table 9 and Figure 8.

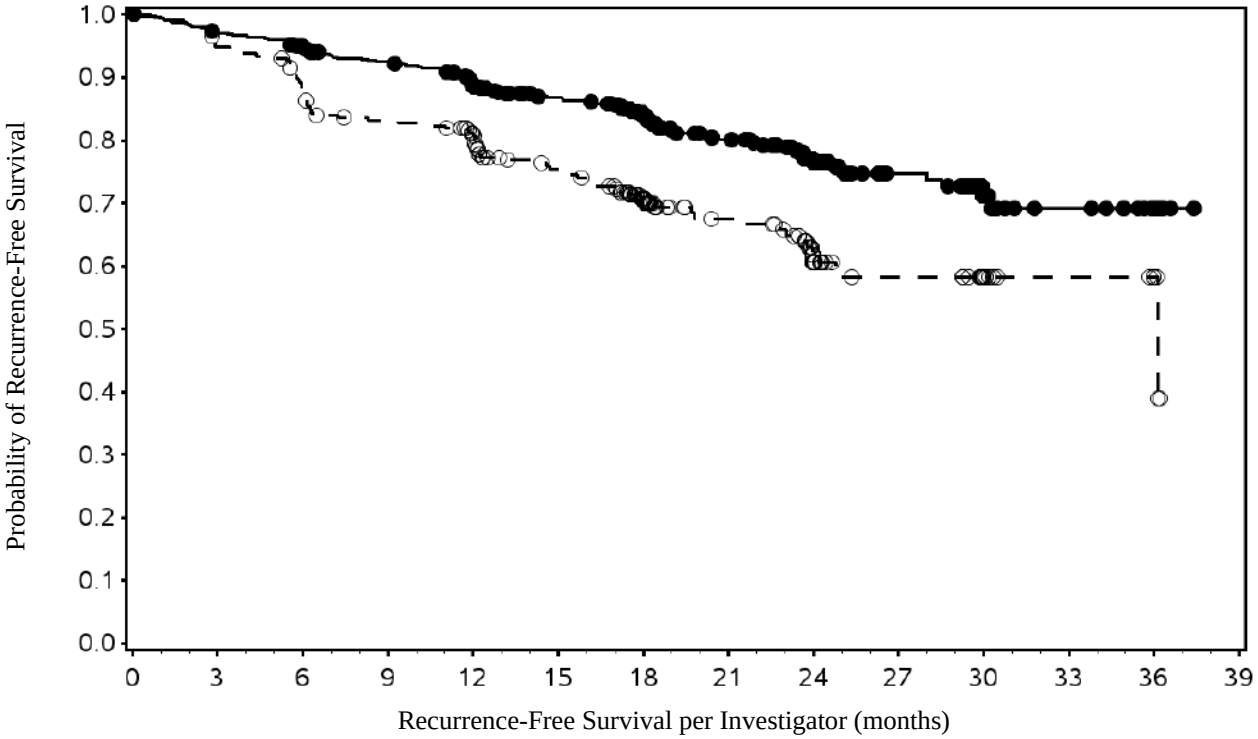
Table 9: Efficacy results (CA20976K)

	nivolumab (n = 526)	**placebo (n = 264)**
Recurrence-free survival with minimum follow-up 15.6 months		
Recurrence-free survival		
Events	102 (19.4%)	84 (31.8%)
Hazard ratio[a]	0.53	
95% CI	(0.40, 0.71)	
Median (95% CI) months	NR	36.14 (24.77, NR)
Rate (95% CI) at 12 months[b]	88.8 (85.6, 91.2)	81.1 (75.7, 85.4)
Rate (95% CI) at 18 months[b]	83.9 (80.3, 86.9)	70.7 (64.5, 76.1)

[a] Based on stratified Cox proportional hazard model.
[b] Based on Kaplan-Meier estimates.

RFS benefit was consistent across key subgroups, including disease stage, T-category, and age.

Figure 8: Recurrence-free survival (CA20976K)



Number of subjects at risk

Nivolumab													
526	492	474	456	422	386	291	210	122	74	40	22	13	0
Placebo													
264	244	224	208	193	165	120	77	44	25	12	7	4	0

----●---- Nivolumab (events 102/526), median and 95% CI: NR
- - -❍- - - Placebo (events: 84/264), median and 95% CI: 36.14 (24.77, NR)
Nivolumab vs. Placebo – HR (95% CI): 0.53 (0.40, 0.71)
Based on data cut-off: 21-February-2023, minimum follow-up of 15.6 months

Tumour PD-L1 expression data were available for 302/790 (38.2%) randomised patients (36.3% and 42.0% in the nivolumab and placebo arms, respectively), as PD-L1 expression was not a stratification factor for randomisation. The exploratory RFS analyses by PD-L1 expression showed a HR for nivolumab vs placebo of 0.43 (95% CI: 0.22, 0.84) in patients (N = 167) with PD-L1 expression ≥ 1%, 0.82 (95% CI: 0.44, 1.54) in patients (N = 135) with PD-L1 expression < 1%, and 0.50 (95% CI: 0.34, 0.73) in patients (N = 488) with indeterminate/not reported/not evaluable PD-L1 expression.

Intravenous formulation

Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA209238). The study included adult patients, who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7th edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumour PD-L1 status. Patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomised to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomisation was stratified by tumour PD-L1 expression (≥ 5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumour assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

Baseline characteristics were generally balanced between the two groups. The median age was 55 years (range: 18-86), 58% were men, and 95% were white. Baseline ECOG performance status score was 0 (90%) or 1 (10%). The majority of patients had AJCC Stage III disease (81%), and 19% had Stage IV disease. Forty-eight percent of patients had macroscopic lymph nodes and 32% had tumour ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and 13% BRAF were status unknown. For tumour PD-L1 expression, 34% of patients had PD-L1 expression ≥ 5% and 62% had < 5% as determined by clinical trial assay. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

At a primary pre-specified interim analysis (minimum follow-up 18 months) a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51, 0.83; stratified log-rank p < 0.0001) was demonstrated. At an updated descriptive RFS analysis, with minimum follow-up of 24 months RFS improvement was confirmed with HR of 0.66 (95% Cl: 0.54, 0.81; p < 0.0001) and OS was not mature. Efficacy results with minimum follow-up of 36 months (RFS pre-specified final analysis) and 48 months (OS pre-specified final analysis) are shown in Table 10 and Figures 9 and 10 (all randomised population).

Table 10: Efficacy results (CA209238)

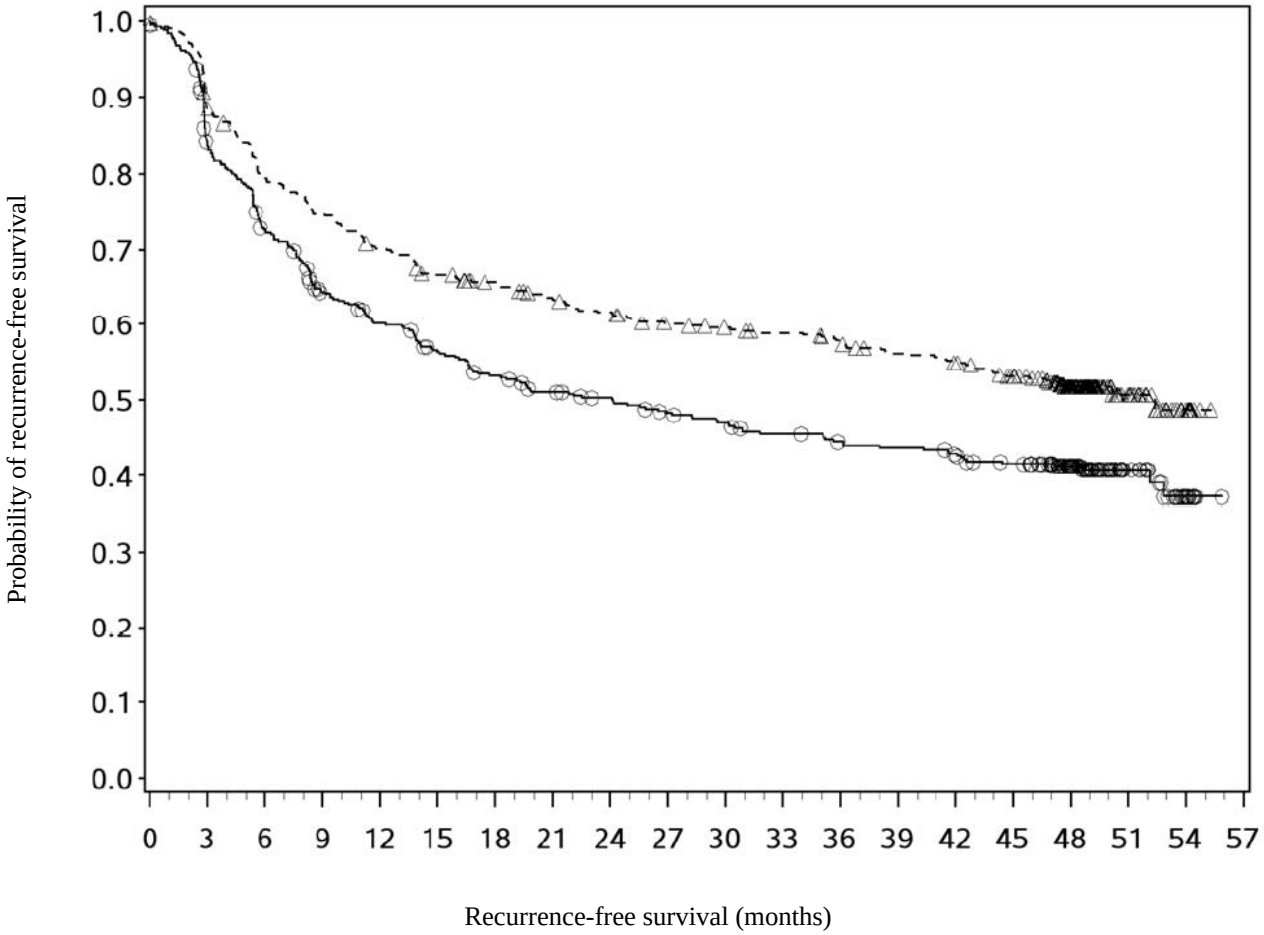
	nivolumab (n = 453)	**ipilimumab 10 mg/kg (n = 453)**
Final pre-specified analysis Recurrence-free survival with minimum follow-up 36 months		
Events	188 (41.5%)	239 (52.8%)
Hazard ratio[a]	0.68	
95% CI	(0.56, 0.82)	
p-value	p < 0.0001	
Median (95% CI) months	NR (38.67, NR)	24.87 (16.62, 35.12)
Recurrence-free survival with minimum follow-up 48 months		
Events	212 (46.8%)	253 (55.8%)
Hazard ratio[a]	0.71	
95% CI	(0.60, 0.86)	
Median (95% CI) months	52.37 (42.51, NR)	24.08 (16.56, 35.09)
Rate (95% CI) at 12 months	70.4 (65.9, 74.4)	60.0 (55.2, 64.5)
Rate (95% CI) at 18 months	65.8 (61.2, 70.0)	53.0 (48.1, 57.6)
Rate (95% CI) at 24 months	62.6 (57.9, 67.0)	50.2 (45.3, 54.8)
Rate (95% CI) at 36 months	57.6 (52.8, 62.1)	44.4 (39.6, 49.1)
Rate (95% CI) at 48 months	51.7 (46.8, 56.3)	41.2 (36.4, 45.9)

	nivolumab (n = 453)	ipilimumab 10 mg/kg (n = 453)
Final pre-specified analysis Overall survival with minimum follow-up 48 months		
Events	100 (22.1%)	111 (24.5%)
Hazard ratio[a]	0.87	
95.03% CI	(0.66, 1.14)	
p-value	0.3148	
Median (95% CI) months	Not Reached	Not Reached
Rate (95% CI) at 12 months	96.2 (93.9, 97.6)	95.3 (92.8, 96.9)
Rate (95% CI) at 18 months	91.9 (88.9, 94.1)	91.8 (88.8, 94.0)
Rate (95% CI) at 24 months	88.0 (84.6, 90.7)	87.8 (84.4, 90.6)
Rate (95% CI) at 36 months	81.7 (77.8, 85.1)	81.6 (77.6, 85.0)
Rate (95% CI) at 48 months	77.9 (73.7, 81.5)	76.6 (72.2, 80.3)

[a] Derived from a stratified proportional hazards model.

With a minimum follow-up of 36 months, the trial demonstrated a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease. With a minimum follow up of 48 months, shown in Figure 9, the trial continued to demonstrate improvement in RFS in the nivolumab arm compared with the ipilimumab arm. RFS benefit was sustained across all subgroups.

Figure 9: Recurrence-free survival (CA209238)

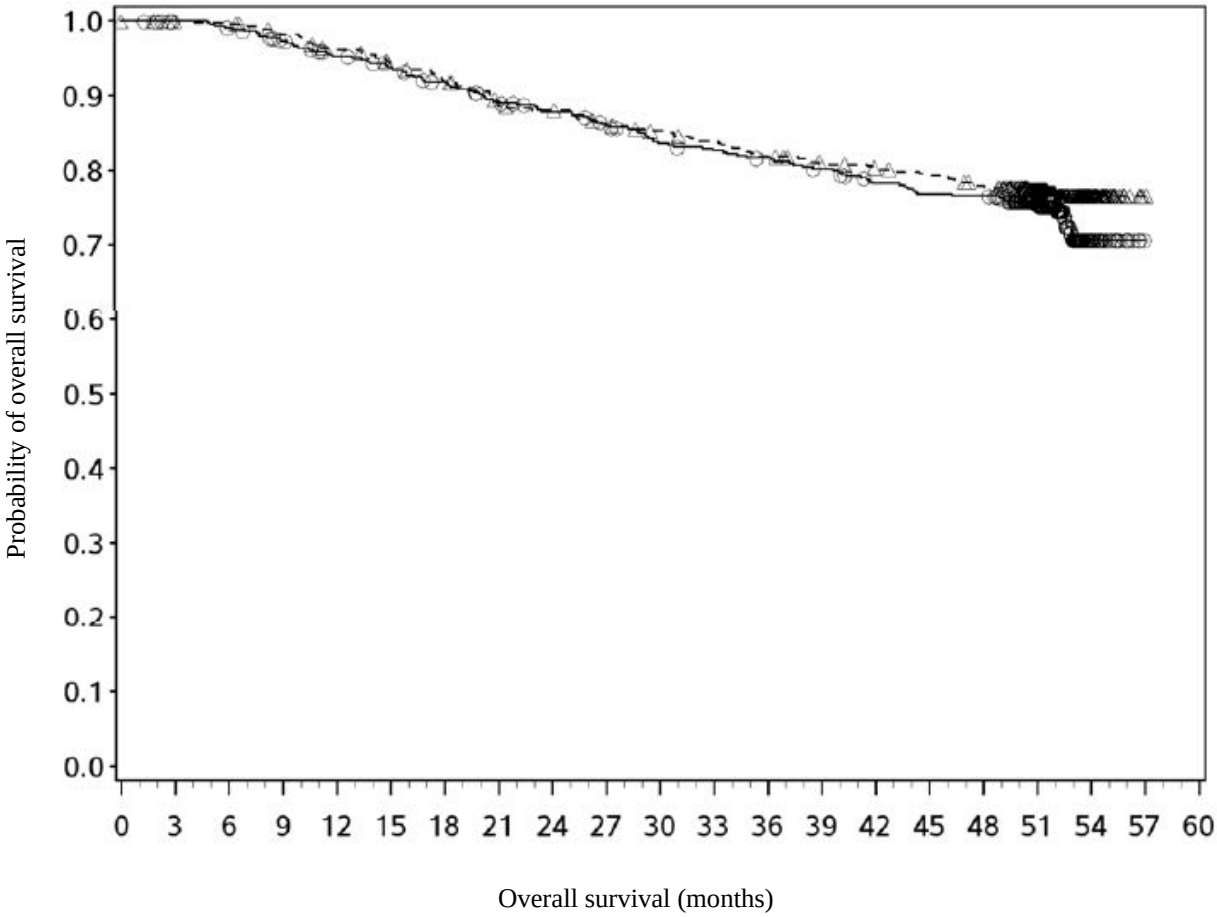


Number of subjects at risk

Nivolumab																				
453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0	
Ipilimumab																				
453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0	

- - -△- - - Nivolumab ---❍---- Ipilimumab

Figure 10: Overall survival (CA209238)



Number of subjects at risk

Nivolumab																				
453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	237	45	1	0
Ipilimumab																				
453	447	442	430	416	407	395	382	373	363	350	345	340	333	322	316	315	218	40	0	0

- - -△- - - Nivolumab ---❍---- Ipilimumab

With a minimum follow-up of 48 months, shown in Figure 10, median OS was not reached in either group (HR = 0.87, 95.03% CI: 0.66, 1.14; p-value: 0.3148). The overall survival data are confounded by the effects of effective subsequent anti-cancer therapies. Subsequent systemic therapy was received by 33% and 42% of patients in the nivolumab and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 23% and 34% of patients in the nivolumab and ipilimumab arms, respectively.

Quality of life (QoL) with nivolumab remained stable and close to baseline values during treatment, as assessed by valid and reliable scales like the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EQ-5D utility index and visual analog scale (VAS).

Non-small cell lung cancer

Treatment of NSCLC after prior chemotherapy

Squamous NSCLC

Intravenous formulation

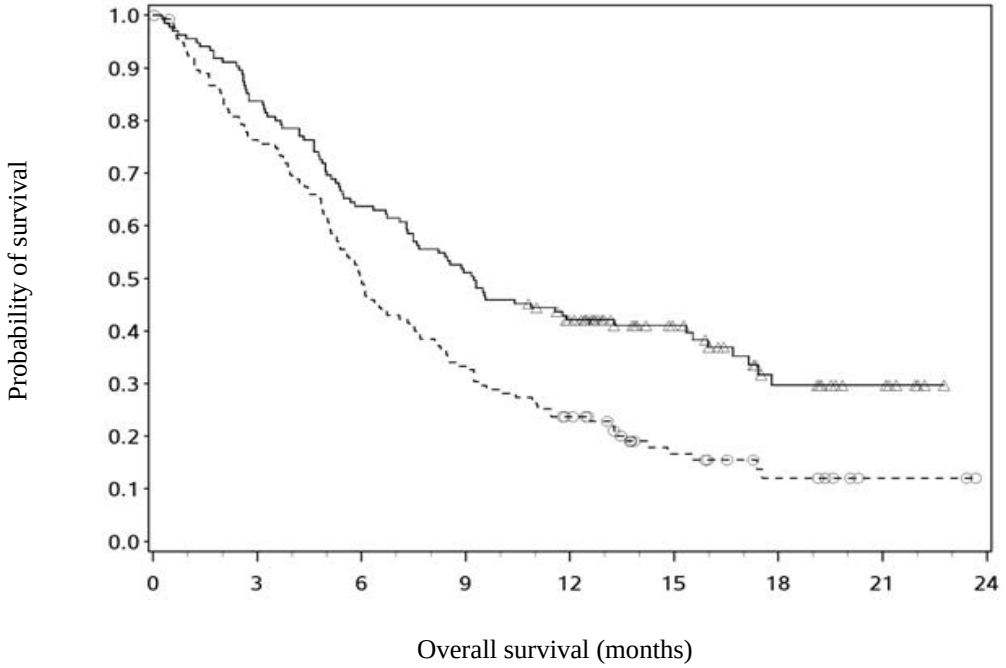
Randomised phase 3 study vs. docetaxel (CA209017)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the RECIST, version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung cancer symptom score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥ 65 years of age and 11% ≥ 75 years of age. The majority of patients were white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status score was 0 (24%) or 1 (76%).

The Kaplan-Meier curves for OS are shown in Figure 11.

Figure 11: Kaplan-Meier curves of OS (CA209017)



Number of subjects at risk

Nivolumab 3 mg/kg								
135	113	86	69	52	31	15	7	0
Docetaxel								
137	103	68	45	30	14	7	2	0

----△---- Nivolumab 3 mg/kg (events: 86/135), median and 95% CI: 9.23 (7.33, 13.27)
- - -❍- - - Docetaxel (events: 113/137), median and 95% CI: 6.01 (5.13, 7.33)

The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated. With a minimum of 62.6 months follow-up, OS benefit remains consistently demonstrated across subgroups.

Study CA209017 included a limited number of patients ≥ 75 years (11 in the nivolumab group and 18 in the docetaxel group). Nivolumab showed numerically less effect on OS (HR 1.85; 95% CI: 0.76, 4.51), PFS (HR = 1.76; 95%-CI: 0.77, 4.05) and ORR (9.1% vs. 16.7%). Because of the small sample size, no definitive conclusions can be drawn from these data.

Efficacy results are shown in Table 11.

Table 11: Efficacy results (CA209017)

	nivolumab (n = 135)		docetaxel (n = 137)
Primary analysis Minimum follow-up: 10.6 months			
Overall survival			
Events	86 (63.7%)		113 (82.5%)
Hazard ratio		0.59	
96.85% CI		(0.43, 0.81)	
p-value		0.0002	
Median (95% CI) months	9.23 (7.33, 13.27)		6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1 (33.7, 50.3)		23.7 (16.9, 31.1)
Confirmed objective response	27 (20.0%)		12 (8.8%)
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Odds ratio (95% CI)		2.64 (1.27, 5.49)	
p-value		0.0083	
Complete response (CR)	1 (0.7%)		0
Partial response (PR)	26 (19.3%)		12 (8.8%)
Stable disease (SD)	39 (28.9%)		47 (34.3%)
Median duration of response			
Months (range)	Not reached (2.9-20.5^{+})		8.4 (1.4^{+}-15.2^{+})
Median time to response			
Months (range)	2.2 (1.6-11.8)		2.1 (1.8-9.5)
Progression-free survival			
Events	105 (77.8%)		122 (89.1%)
Hazard ratio		0.62	
95% CI		(0.47, 0.81)	
p-value		< 0.0004	
Median (95% CI) (months)	3.48 (2.14, 4.86)		2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)		6.4 (2.9, 11.8)
Updated analysis Minimum follow-up: 24.2 months			
Overall survival[a]			
Events	110 (81.4%)		128 (93.4%)
Hazard ratio		0.62	
95% CI		(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)		8 (4.3, 13.3)
Confirmed objective response	20.0%		8.8%
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Median duration of response			
Months (range)	25.2 (2.9-30.4)		8.4 (1.4^{+}-18.0^{+})

	nivolumab (n = 135)		docetaxel (n = 137)
Progression-free survival			
Rate (95% CI) at 24 months	15.6 (9.7, 22.7)		All patients had either progressed, were censored, or lost to follow-up
Updated analysis Minimum follow-up: 62.6 months			
Overall survival[a]			
Events	118 (87.4%)		133 (97.1%)
Hazard ratio		0.62	
95% CI		(0.48, 0.79)	
Rate (95% CI) at 60 months	12.3 (7.4, 18.5)		3.6 (1.4, 7.8)
Confirmed objective response	20.0%		8.8%
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Median duration of response			
Months (range)	25.2 (2.9-70.6+)		7.5 (0.0+-18.0+)
Progression-free survival			
Rate (95% CI) at 60 months	9.4 (4.8, 15.8)		All patients had either progressed, were censored, or lost to follow-up

[a] Six patients (4%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" Denotes a censored observation.

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

Intravenous formulation

Single-arm phase 2 study (CA209063)
Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an ORR of 14.5% (95% CI: 8.7,22.2%), a median OS of 8.21 months (95% CI: 6.05,10.9), and a median PFS of 1.87 months (95% CI 1.77,3.15). The PFS was measured by RECIST, version 1.1. The estimated 1-year survival rate was 41%.

Intravenous formulation

Single-arm phase 2 study (CA209171)
Study CA209171 was a single-arm, open label study of nivolumab monotherapy in patients with previously treated advanced or metastatic squamous NSCLC. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 811 treated patients, 103 (13%) had an ECOG performance score of 2, 686 (85%) were < 75 years old and 125 (15%) were ≥ 75 years old. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed ORR are presented in Table 12 below.

Table 12: ORR based on response evaluable patients – total and by subgroup (CA209171)

Results	Total	ECOG PS 2	< 75 years	≥ 75 years
N responders/ N evaluable[a]	66/671	1/64	55/568	11/103
(%)	(9.8)	(6.1)	(9.7)	(10.7)
95% CI[b]	(7.7, 12.3)	(0.0, 8.4)	(7.4, 12.4)	(5.5, 18.3)

[a] includes confirmed and unconfirmed responses, scans were mandatory only at week 8/9 and week 52.
[b] CR+PR, confidence interval based on the Clopper and Pearson method

Non-squamous NSCLC

Intravenous formulation

Randomised phase 3 study vs. docetaxel (CA209057)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

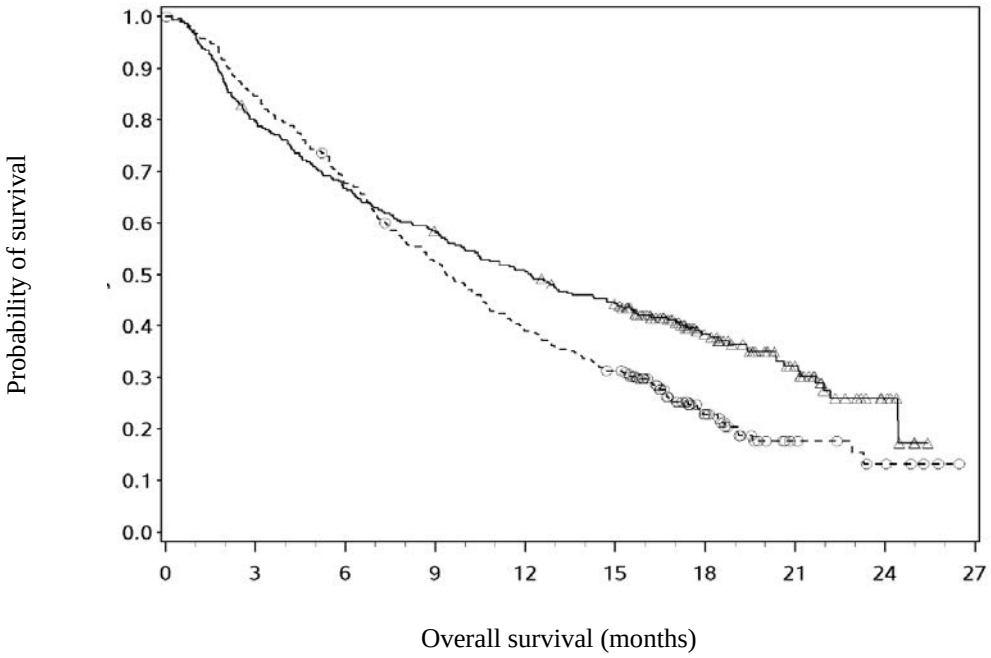
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m^2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted according to the RECIST version 1.1. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy of tumour PD-L1 expression at predefined levels of 1%, 5% and 10%. Assessment according to discrete PD-L1 expression intervals were not included in the prespecified analyses due to the small sample sizes within the intervals.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

The median age was 62 years (range: 21 to 85) with 34% ≥ 65 years of age and 7% ≥ 75 years of age. The majority of patients were white (92%) and male (55%). Baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The Kaplan-Meier curves for OS are shown in Figure 12.

Figure 12: Kaplan-Meier curves of OS (CA209057)



Number of subjects at risk

Nivolumab 3 mg/kg									
292	232	194	169	146	123	62	32	9	0
Docetaxel									
290	244	194	150	111	88	34	10	5	0

----△---- Nivolumab 3 mg/kg (events: 190/292), median and 95% CI: 12.19 (9.66, 14.98)
- - -❍- - - Docetaxel (events: 223/290), median and 95% CI: 9.36 (8.05, 10.68)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 13.

Table 13: Efficacy results (CA209057)

	nivolumab (n = 292)	**docetaxel (n = 290)**
Prespecified interim analysis Minimum follow-up: 13.2 months		
Overall survival		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)

	nivolumab (n = 292)	docetaxel (n = 290)
Confirmed objective response	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response		
Months (range)	17.15 (1.8-22.6+)	5.55 (1.2+-15.2+)
Median time to response		
Months (range)	2.10 (1.2-8.6)	2.61 (1.4-6.3)
Progression-free survival		
Events	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[c]		
Events	228 (78.1%)	247 (85.1%)
Hazard ratioa	0.75	
(95% CI)	(0.63, 0.91)	
Rate (95% CI) at 24 months	28.7 (23.6, 34.0)	15.8 (11.9, 20.3)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-33.7+)	5.6 (1.2+-16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9 (8.3, 16.2)	1.0 (0.2, 3.3)
Updated analysis Minimum follow-up: 62.7 months		
Overall survival[d]		
Events	250 (85.6%)	279 (96.2%)
Hazard ratio[a]	0.70	
(95% CI)	(0.58, 0.83)	
Rate (95% CI) at 60 months	14.0 (10.2, 18.3)	2.1 (0.9, 4.4)

	nivolumab (n = 292)	docetaxel (n = 290)
Confirmed objective response	19.5%	12.4%
(95% CI)	(15.1, 24.5)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-70.4[+])	5.6 (0.0[+]-33.4)
Progression-free survival		
Rate (95% CI) at 60 months	7.5 (4.5, 11.4)	All patients had either progressed, were censored, or lost to follow-up

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.
[c] Sixteen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
[d] Seventeen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" Denotes a censored observation.

Quantifiable tumour PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. docetaxel) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (53% vs. 55%), ≥ 5% (41% vs. 38%), or ≥ 10% (37% vs. 35%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to docetaxel, whereas survival was similar to docetaxel in patients with low or no tumour PD-L1 expression. In terms of ORR, increasing PD-L1 expression was associated with larger ORR. Comparable to the overall population, median duration of response was increased with nivolumab vs. docetaxel for patients with no PD-L1 expression (18.3 months vs. 5.6 months) and for patients with PD-L1 expression (16.0 months vs. 5.6 months).

Table 14 summarises results of ORR and OS by tumour PD-L1 expression.

Table 14: ORR and OS by tumour PD-L1 expression (CA209057)

PD-L1 expression	nivolumab	docetaxel	
	ORR by tumour PD-L1 expression Minimum follow-up: 13.2 months		
			Odds ratio (95% CI)
< 1%	10/108 (9.3%) 95% CI: 4.5, 16.4	15/101 (14.9%) 95% CI: 8.6, 23.3	0.59 (0.22, 1.48)
≥ 1%	38/123 (30.9%) 95% CI: 22.9, 39.9	15/123 (12.2%) 95% CI: 7.0, 19.3	3.22 (1.60, 6.71)
≥ 1% to < 10%[a]	6/37 (16.2%) 95% CI: 6.2, 32.0	5/44 (11.4%) 95% CI: 3.8, 24.6	1.51 (0.35, 6.85)
≥ 10% to < 50%[a]	5/20 (25.0%) 95% CI: 8.7, 49.1	7/33 (21.2%) 95% CI: 9.0, 38.9	1.24 (0.26, 5.48)
≥ 50%[a]	27/66 (40.9%) 95% CI: 29.0, 53.7	3/46 (6.5%) 95% CI: 1.4, 17.9	9.92 (2.68, 54.09)

PD-L1 expression	nivolumab	docetaxel	
	OS by tumour PD-L1 expression		
	Minimum follow-up: 13.2 months		
	Number of events (number of patients)		**Unstratified hazard ratio (95% CI)**
< 1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥ 1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥ 1% to < 10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥ 10% to < 50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥ 50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)
	Updated analysis		
	Minimum follow-up: 24.2 months		
< 1%	91 (108)	86 (101)	0.91 (0.67, 1.22)
≥ 1%	87 (123)	103 (123)	0.62 (0.47, 0.83)
	Updated analysis		
	Minimum follow-up: 62.7 months		
< 1%	100 (109)	96 (101)	0.87 (0.66, 1.16)
≥1%	96 (122)	119 (123)	0.55 (0.42, 0.73)

[a] Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels.

A higher proportion of patients experienced death within the first 3 months in the nivolumab arm (59/292, 20.2%) as compared to the docetaxel arm (44/290, 15.2%). Results of a post-hoc, exploratory multivariate analysis indicated that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower (e.g., < 50%) or no tumour PD-L1 expression may be at higher risk of death within the first 3 months.

In subgroup analyses, survival benefit compared to docetaxel was not shown for patients who were never-smokers or whose tumours harboured EGFR activating mutations; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Renal cell carcinoma (RCC)

Subcutaneous formulation

Randomised, open-label phase 3 study vs. intravenous nivolumab (CA20967T)
The safety and efficacy of nivolumab subcutaneous formulation was evaluated in a multicentre, randomised, open-label study in patients with advanced or metastatic clear cell RCC (CA20967T). Patients 18 years of age or older with histologically confirmed advanced or metastatic RCC with a clear cell component, including those with sarcomatoid features, and who received no more than 2 prior systemic treatment regimens were randomised to receive nivolumab 1200 mg every 4 weeks subcutaneously or nivolumab 3 mg/kg every 2 weeks intravenously. Patients with untreated, symptomatic CNS metastases; leptomeningeal metastases; concurrent malignancies requiring treatment or history of prior malignancy within the prior 2 years; active, known, or suspected autoimmune disease; or who received prior treatment with a checkpoint inhibitor were excluded from the study. Patients with asymptomatic, stable CNS metastases that did not require immediate treatment were eligible if there was no evidence of progression within 28 days prior to the first dose of study drug administration.

Stratification factors for randomisation were weight (< 80 kg vs ≥ 80 kg) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification (favourable vs intermediate vs poor risk).

The primary objective of the study was to demonstrate noninferiority of the serum nivolumab C_{avgd28} and C_{minss} for the subcutaneous administration of nivolumab to the intravenous administration of nivolumab (see section 5.2). The key secondary objective of the study was to demonstrate noninferiority of the ORR for the subcutaneous administration of nivolumab to the intravenous administration of nivolumab, as assessed by blinded independent central review (BICR). Additional secondary objectives included assessing duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

A total of 495 patients were randomised to receive either subcutaneous nivolumab (n = 248) or intravenous nivolumab (n = 247). The median age was 65 years (range: 20 to 93), with 51% ≥ 65 years of age and 14% ≥ 75 years of age, 85% White, 0.8% Asian, and 0.4% Black, and 68% male. Fifty-seven percent of patients weighed < 80 kg and 43% weighed ≥ 80 kg. Baseline Karnofsky performance status was 70 (7%), 80 (20%), 90 (34%), or 100 (39%). Patient distribution by IMDC risk categories was 21% favourable, 62% intermediate, and 17% poor.

The study demonstrated noninferiority of nivolumab 1200 mg administered subcutaneously to nivolumab 3 mg/kg administered intravenously (see section 5.2). At the primary analysis (minimum follow-up of 8 months) ORR was 24.2% (95% CI: 19.0, 30.0) for subcutaneous nivolumab and 18.2% (95% CI: 13.6, 23.6) for intravenous nivolumab. The estimate of objective response risk ratio was 1.33 (95% CI: 0.94, 1.88). To declare noninferiority, the lower bound of the two-sided 95% CI of the objective response risk ratio had to be ≥ 0.60. Updated efficacy results with a minimum follow-up of 14.9 months (data cut-off 21-Feb-2024) are shown in Table 15.

Table 15: Efficacy results - CA20967T

	Subcutaneous nivolumab	**Intravenous nivolumab**
ORR[a] per BICR % (n/N)	26.6% (66/248)	20.6% (51/247)
95% CI[b]	(21.2, 32.6)	(15.8, 26.2)
Estimate of objective response risk ratio (95% CI)[c, d]	1.28 (0.93, 1.77)	
DORa per BICR Median, months (95% CI)[e]	13.57 (8.57, NE)	NR (15.7, NE)
PFS[e] per BICR %, events (n/N)	68.1% (169/248)	67.2% (166/247)
Median, months (95% CI)[f]	6.34 (5.13, 7.49)	5.65 (5.19, 7.39)

NR = not reached, NE = non-estimable

[a] Descriptive analysis.

[b] Confidence interval based on the Clopper and Pearson method.

[c] Stratified by weight (< 80 kg vs ≥ 80 kg) and IMDC risk group (favourable vs intermediate vs poor).

[d] Strata adjusted risk ratio (subcutaneous nivolumab over intravenous nivolumab using Mantel-Haenszel method).

[e] Median computed using Kaplan-Meier method.

Intravenous formulation

Randomised phase 3 study of nivolumab as monotherapy vs. everolimus (CA209025)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced RCC with a clear cell component was evaluated in a Phase 3, randomised, open-label study (CA209025). The study included patients (18 years or older) who have experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥ 70%. This study included patients regardless of their tumour PD-L1 status. Patients with any history of or concurrent brain metastases, prior treatment with a mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

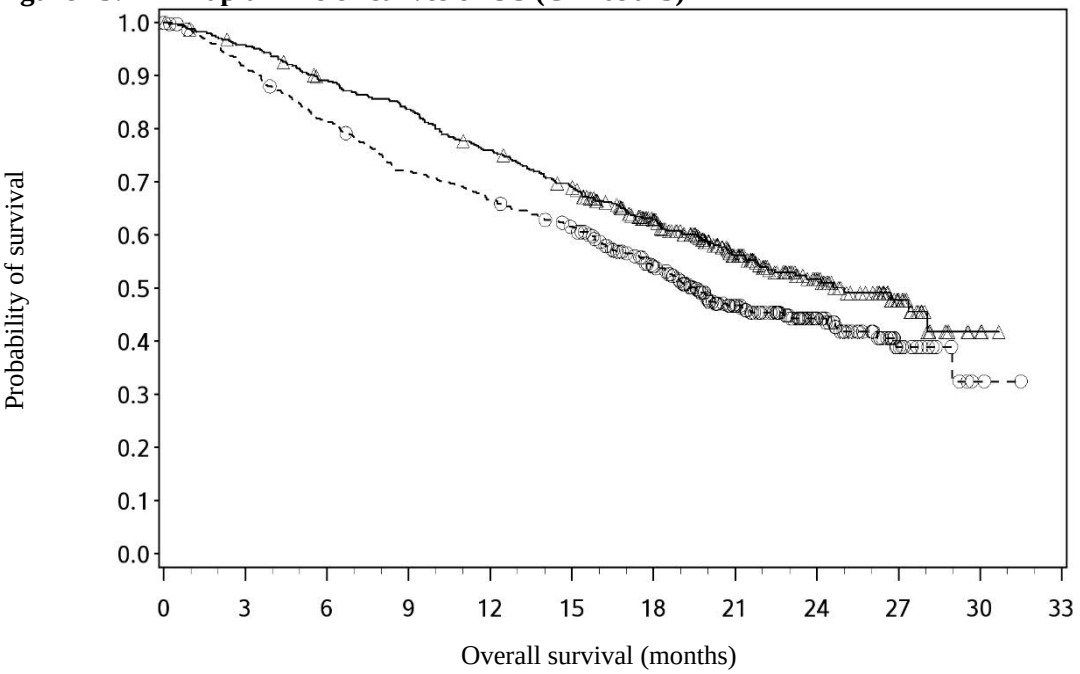
A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n = 410) administered intravenously over 60 minutes every 2 weeks or everolimus (n = 411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after randomisation and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥ 65 years of age and 9% ≥ 75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 13.

Figure 13: Kaplan-Meier curves of OS (CA209025)



Number of subjects at risk

Nivolumab											
410	389	359	337	305	275	213	139	73	29	3	0
Everolimus											
411	366	324	287	265	241	187	115	61	20	2	0

----△---- Nivolumab 3 mg/kg (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
- - -❍- - - Everolimus 10 mg (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 16 and Figure 13). OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 16.

Table 16: Efficacy results (CA209025)

	nivolumab (n = 410)		**everolimus (n = 411)**
Overall survival			
Events	183 (45%)		215 (52%)
Hazard ratio		0.73	
98.52% CI		(0.57, 0.93)	
p-value		0.0018	
Median (95% CI)	25.0 (21.7, NE)		19.6 (17.6, 23.1)
Rate (95% CI)			
At 6 months	89.2 (85.7, 91.8)		81.2 (77.0, 84.7)
At 12 months	76.0 (71.5, 79.9)		66.7 (61.8, 71.0)
Objective response	103 (25.1%)		22 (5.4%)
(95% CI)	(21.0, 29.6)		(3.4, 8.0)
Odds ratio (95% CI)		5.98 (3.68, 9.72)	
p-value		< 0.0001	
Complete response (CR)	4 (1.0%)		2 (0.5%)
Partial response (PR)	99 (24.1%)		20 (4.9%)
Stable disease (SD)	141 (34.4%)		227 (55.2%)
Median duration of response			
Months (range)	11.99 (0.0-27.6^{+})		11.99 (0.0^{+}-22.2^{+})
Median time to response			
Months (range)	3.5 (1.4-24.8)		3.7 (1.5-11.2)
Progression-free survival			
Events	318 (77.6%)		322 (78.3%)
Hazard ratio		0.88	
95% CI		(0.75, 1.03)	
p-value		0.1135	
Median (95% CI)	4.6 (3.71, 5.39)		4.4 (3.71, 5.52)

"+" denotes a censored observation.
NE = non-estimable

The median time to onset of objective response was 3.5 months (range: 1.4-24.8 months) after the start of nivolumab treatment. Forty-nine (47.6%) responders had ongoing responses with a duration ranging from 0.0-27.6^{+} months.

Overall survival could be accompanied by an improvement over time in disease related symptoms and non-disease specific QoL as assessed using valid and reliable scales in the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and the EuroQoL EQ-5D. Apparently meaningful symptom improvement (MID = 2 point change in FKSI-DRS score;

p < 0.001) and time to improvement (HR = 1.66 (1.33, 2.08), p < 0.001) were significantly better for patients on the nivolumab arm. While both arms of the study received active therapy, the QoL data should be interpreted in the context of the open-label study design and therefore cautiously taken.

Intravenous formulation

Phase 3b/4 safety study (CA209374)
Additional safety and descriptive efficacy data are available from study CA209374, an open-label Phase 3b/4 safety study of nivolumab monotherapy (treated with 240 mg every 2 weeks) for the treatment of patients with advanced or metastatic RCC (n = 142), including 44 patients with non-clear cell histology.

In subjects with non-clear cell histology, at a minimum follow-up of approximately 16.7 months ORR and median duration of response were 13.6% and 10.2 months, respectively. Clinical activity was observed regardless of tumour PD-L1 expression status.

Intravenous formulation

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. sunitinib (CA209214)
The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomisation, Karnofsky performance status < 80%, haemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal). This study included patients regardless of their tumour PD-L1 status. Patients with Karnofsky performance status < 70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by IMDC prognostic score and region.

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n = 422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 12 weeks after randomisation and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a BICR in intermediate/poor risk patients.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 21-85) with 38% ≥ 65 years of age and 8% ≥ 75 years of age. The majority of patients were male (73%) and white (87%), and 31% and 69% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The median duration of time from initial diagnosis to randomisation was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day-21.4+ months) in nivolumab with ipilimumab-treated patients and was 7.8 months (range: 1 days-20.2+ months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.

Efficacy results for the intermediate/poor risk patients are shown in Table 17 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 14 (minimum follow-up of 60 months).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis.

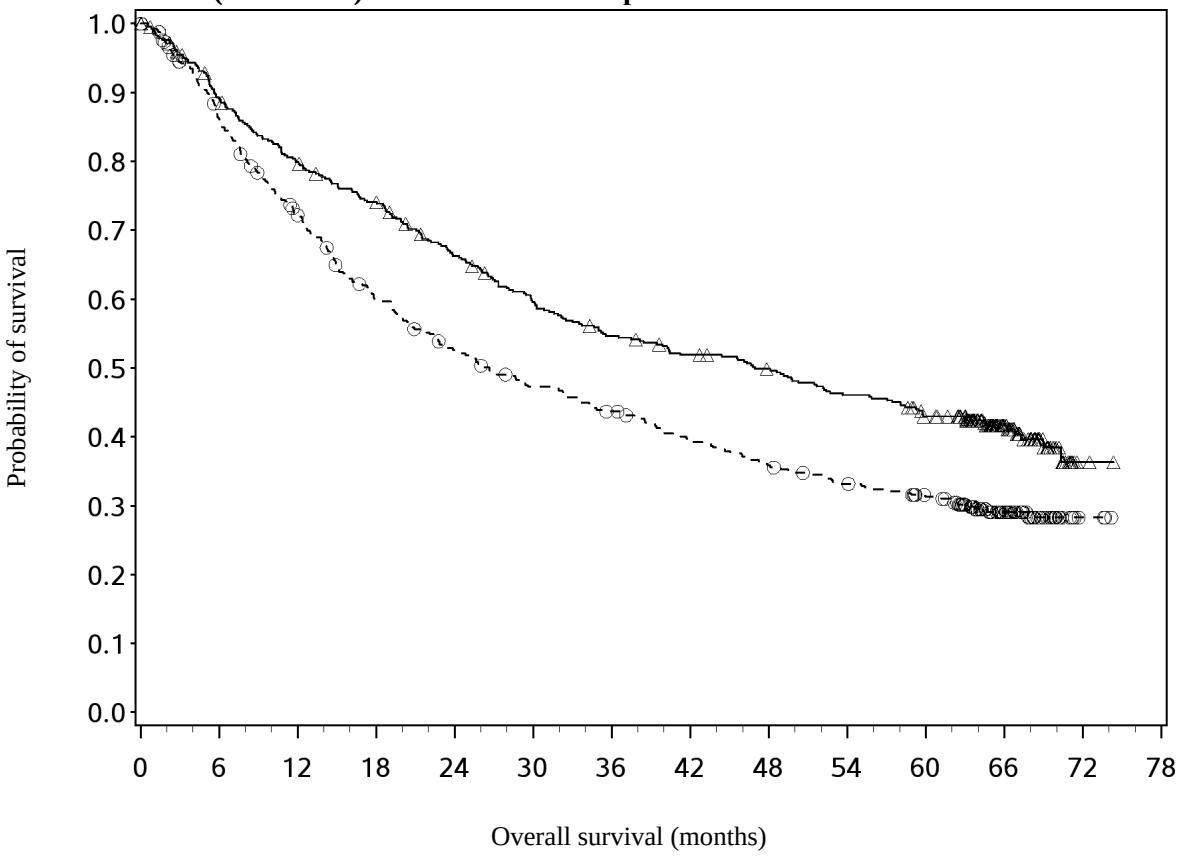
Table 17: Efficacy results in intermediate/poor risk patients (CA209214)

	nivolumab + ipilimumab (n = 425)		**sunitinib (n = 422)**
	Primary analysis minimum follow-up: 17.5 months		
Overall survival			
Events	140 (33%)		188 (45%)
Hazard ratio[a]		0.63	
99.8% CI		(0.44, 0.89)	
p-value[b, c]		< 0.0001	
Median (95% CI)	NE (28.2, NE)		25.9 (22.1, NE)
Rate (95% CI)			
At 6 months	89.5 (86.1, 92.1)		86.2 (82.4, 89.1)
At 12 months	80.1 (75.9, 83.6)		72.1 (67.4, 76.2)
Progression-free survival			
Events	228 (53.6%)		228 (54.0%)
Hazard ratio[a]		0.82	
99.1% CI		(0.64, 1.05)	
p-value[b,h]		0.0331	
Median (95% CI)	11.6 (8.71, 15.51)		8.4 (7.03, 10.81)
Confirmed objective response (BICR)	177 (41.6%)		112 (26.5%)
(95% CI)	(36.9, 46.5)		(22.4, 31.0)
Difference in ORR (95% CI)[d]		16.0 (9.8, 22.2)	
p-value[e,f]		< 0.0001	
Complete response (CR)	40 (9.4%)		5 (1.2%)
Partial response (PR)	137 (32.2%)		107 (25.4%)
Stable disease (SD)	133 (31.3%)		188 (44.5%)
Median duration of response[g]			
Months (range)	NE (1.4^{+}-25.5^{+})		18.17 (1.3^{+}-23.6^{+})
Median time to response			
Months (range)	2.8 (0.9-11.3)		3.0 (0.6-15.0)
	Updated analysis* minimum follow-up: 60 months		
Overall survival			
Events	242 (57%)		282 (67%)
Hazard ratio[a]		0.68	
95% CI		(0.58, 0.81)	

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
Median (95% CI)	46.95 (35.35, 57.43)	26.64 (22.08, 33.54)
Rate (95% CI)		
At 24 months	66.3 (61.5, 70.6)	52.4 (47.4, 57.1)
At 36 months	54.6 (49.7, 59.3)	43.7 (38.7, 48.5)
At 48 months	49.9 (44.9, 54.6)	35.8 (31.1, 40.5)
At 60 months	43.0 (38.1, 47.7)	31.3 (26.8, 35.9)
Progression-free survival		
Events	245 (57.6%)	253 (60.0%)
Hazard ratio[a]	0.73	
95% CI	(0.61, 0.87)	
Median (95% CI)	11.6 (8.44, 16.63)	8.3 (7.03, 10.41)
Confirmed objective response (BICR)	179 (42.1%)	113 (26.8%)
(95% CI)	(37.4, 47.0)	(22.6, 31.3)
Difference in ORR (95% CI)[d,e]	16.2 (10.0, 22.5)	
Complete response (CR)	48 (11.3%)	9 (2.1%)
Partial response (PR)	131 (30.8%)	104 (24.6%)
Stable disease (SD)	131 (30.8%)	187 (44.3%)
Median duration of response[g]		
Months (range)	NE (50.89-NE)	19.38 (15.38-25.10)
Median time to response		
Months (range)	2.8 (0.9-35.0)	3.1 (0.6-23.6)

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Strata adjusted difference.
[e] Based on the stratified DerSimonian-Laird test.
[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[g] Computed using Kaplan-Meier method.
[h] p-value is compared to alpha 0.009 in order to achieve statistical significance.
"+" denotes a censored observation.
NE = non-estimable
***** Descriptive analysis based on data cut-off: 26-Feb-2021.

Figure 14: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214) - Minimum follow-up of 60 months



Number of subjects at risk

Nivolumab + ipilimumab													
425	372	332	306	270	241	220	207	196	181	163	79	2	0
Sunitinib													
422	353	291	237	206	184	169	151	137	125	112	58	3	0

----△---- Nivolumab + ipilimumab (events: 242/425), median and 95.0% CI: 46.95 (35.35, 57.43)
- - -❍- - - Sunitinib (events: 282/422), median and 95.0% CI: 26.64 (22.08, 33.54)

An updated descriptive OS analysis was performed when all patients had a minimum follow-up of 24 months. At the time of this analysis, the hazard ratio was 0.66 (99.8% CI 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression ≥ 1% was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR = 0.52; 95% CI: 0.34, 0.78). For tumour PD-L1 expression < 1%, the median OS was 34.7 months for the nivolumab in combination with ipilimumab, and was 32.2 months in the sunitinib arm (HR = 0.70; 95% CI: 0.54, 0.92).

CA209214 also randomised 249 favourable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. At a minimum of 24 months follow-up, OS in favourable risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710). With 60 months minimum follow-up, the HR for OS was 0.94 (95% CI: 0.65, 1.37).

There are no data on the use of nivolumab in combination with ipilimumab in patients with only a non clear-cell histology in first-line RCC.

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population at a minimum follow-up of 17.5 months. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Intravenous formulation

Randomised phase 3 study of nivolumab in combination with cabozantinib vs. sunitinib (CA2099ER)
The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥ 70%, and measurable disease as per RECIST v1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

A total of 651 patients were randomised to receive either nivolumab 240 mg (n = 323) administered intravenously every 2 weeks in combination with cabozantinib 40 mg once daily orally or sunitinib (n = 328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration for up to 24 months. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. First tumour assessment post-baseline was performed at 12 weeks (± 7 days) following randomisation. Subsequent tumour assessments occurred at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, confirmed by the BICR. The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥ 65 years of age and 9.5% ≥ 75 years of age. The majority of patients were male (73.9%) and white (81.9%). Eight percent of patients were Asian, 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor. For tumour PD-L1 expression, 72.5% of patients had PD-L1 expression < 1% or indeterminate and 24.9% of patients had PD-L1 expression ≥ 1%. 11.5% of patients had tumours with sarcomatoid features. The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in nivolumab with cabozantinib-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 18.

Table 18: Efficacy results (CA2099ER)

	nivolumab + cabozantinib (n = 323)	**sunitinib (n = 328)**
Progression-free survival		
Events	144 (44.6%)	191 (58.2%)
Hazard ratio[a]	0.51	
95% CI	(0.41, 0.64)	
p-value[b, c]	< 0.0001	

	nivolumab + cabozantinib (n = 323)	sunitinib (n = 328)
Median (95% CI)[d]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)
Overall survival		
Events	67 (20.7%)	99 (30.2%)
Hazard ratio[a]	0.60	
98.89% CI	(0.40, 0.89)	
p-value[b,c,e]	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)
Confirmed objective response (BICR)	180 (55.7%)	89 (27.1%)
(95% CI)[f]	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI)[g]	28.6 (21.7, 35.6)	
p-value[h]	< 0.0001	
Complete response (CR)	26 (8.0%)	15 (4.6%)
Partial response (PR)	154 (47.7%)	74 (22.6%)
Stable disease (SD)	104 (32.2%)	138 (42.1%)
Median duration of response[d]		
Months (range)	20.17 (17.31, N.E.)	11.47 (8.31, 18.43)
Median time to response		
Months (range)	2.83 (1.0-19.4)	4.17 (1.7-12.3)

[a] Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.
[b] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥ 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[c] 2-sided p-values from stratified regular log-rank test.
[d] Based on Kaplan-Meier estimates.
[e] Boundary for statistical significance p-value < 0.0111.
[f] CI based on the Clopper and Pearson method.
[g] Strata adjusted difference in objective response rate (nivolumab + cabozantinib - sunitinib) based on DerSimonian and Laird.
[h] 2-sided p-value from CMH test.
NE = non-estimable

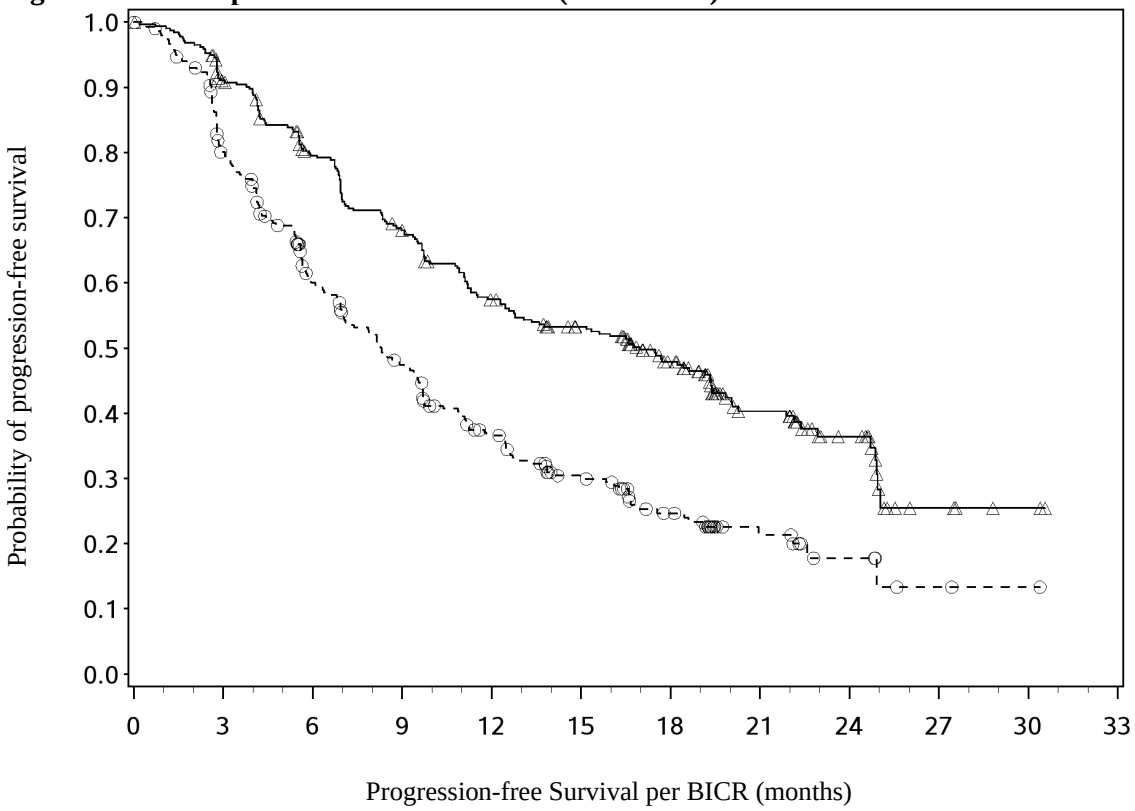
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 18). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of the IMDC risk category. Median PFS for the favourable risk group was not reached for nivolumab in combination with cabozantinib, and was 12.81 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.71 months for nivolumab in combination with cabozantinib and was 8.38 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.29 months for nivolumab in combination with cabozantinib and was 4.21 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of tumour PD-L1 expression. Median PFS for tumour PD-L1 expression ≥ 1% was 13.08 months for nivolumab in combination with cabozantinib, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For tumour PD-L1 expression < 1%, the median PFS was 19.84 months for nivolumab in combination with cabozantinib, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16.0 months and a median follow-up of 23.5 months (see Figures 15 and 16). The PFS hazard ratio was 0.52 (95% CI: 0.43, 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50, 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

Figure 15: Kaplan-Meier curves of PFS (CA2099ER)

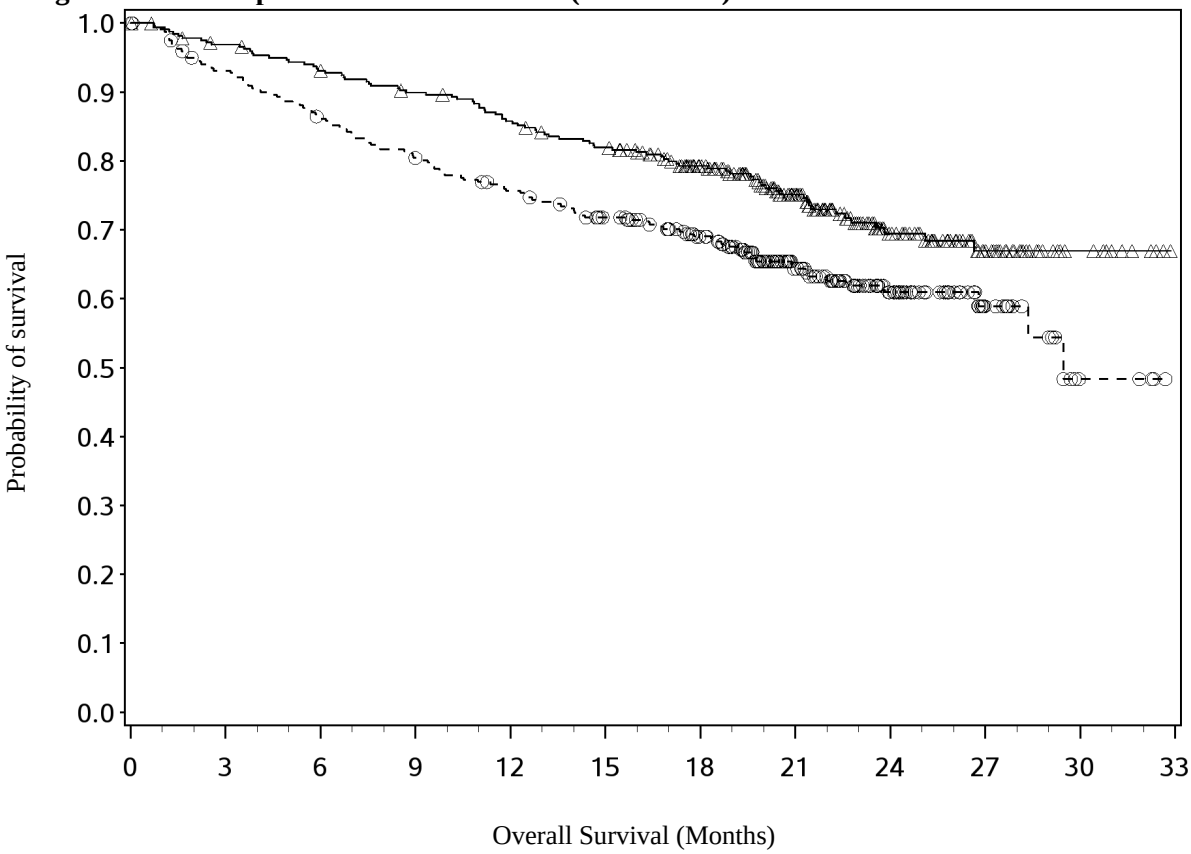


Number of subjects at risk

Nivolumab + cabozantinib											
323	280	236	201	166	145	102	56	26	5	2	0
Sunitinib											
328	230	160	122	87	61	37	17	7	2	1	0

----△---- Nivolumab + cabozantinib (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)
- - -❍- - - Sunitinib (events: 206/328), median and 95.0% CI: 8.31 (6.93, 9.69)

Figure 16: Kaplan-Meier curves of OS (CA2099ER)



Number of subjects at risk

Nivolumab + cabozantinib											
323	308	295	283	269	255	220	147	84	40	10	0
Sunitinib											
328	295	272	254	236	217	189	118	62	22	4	0

----△---- Nivolumab + cabozantinib (events: 86/323), median and 95% CI: NE
- - -❍- - - Sunitinib (events: 116/328), median and 95% CI: 29.47 (28.35, NE)

Squamous cell cancer of the head and neck

Intravenous formulation

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older), with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, recurrent, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or active brain or leptomeningeal metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15),

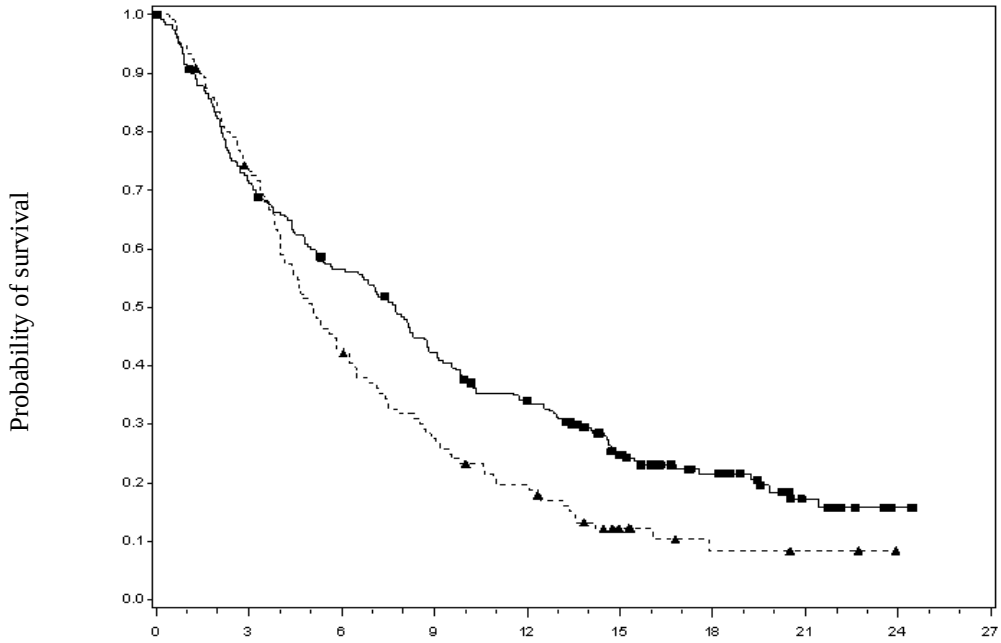
400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly, or docetaxel (n = 54) 30 to 40 mg/m^2 weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted in patients receiving nivolumab, if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 60 years (range: 28-83) with 31% ≥ 65 years of age and 5% ≥ 75 years of age, 83% were male, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 77% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 34% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 17. Efficacy results are shown in Table 19.

Figure 17: Kaplan-Meier curves of OS (CA209141)



Overall survival (months)

Number of subjects at risk

Nivolumab								
240	169	132	98	76	45	27	12	3
Investigator's choice								
121	88	51	32	22	9	4	3	0

—■— Nivolumab 3 mg/kg (events: 184/240), median and 95% CI: 7.72 (5.68, 8.77)
- - -▲- - - Investigator's choice (events: 105/121), median and 95% CI: 5.06 (4.04, 6.24)

Table 19: Efficacy results (CA209141)

	nivolumab (n = 240)	**investigator's choice (n = 121)**
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
Progression-free survival		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.97, 3.12)
Rate (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9, 18.3)
Rate (95% CI) at 12 months	9.5 (6.0, 13.9)	2.5 (0.5, 7.8)

	nivolumab (n = 240)	investigator's choice (n = 121)
Confirmed objective response[c]	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)
Median time to response		
Months (range)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
Median duration of response		
Months (range)	9.7 (2.8-20.3+)	4.0 (1.5+-8.5+)

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.
[c] In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

Quantifiable tumour PD-L1 expression was measured in 67% of patients in the nivolumab group and 82% of patients in the investigator's choice group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. investigator's choice) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (55% vs. 62%), ≥ 5% (34% vs. 43%), or ≥ 10% (27% vs. 34%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (see Table 20).

Table 20: OS by tumour PD-L1 expression (CA209141)

PD-L1 Expression	nivolumab	investigator's choice	
	OS by tumour PD-L1 expression		
	Number of events (number of patients)		Unstratified hazard ratio (95% CI)
< 1%	56 (73)	32 (38)	0.83 (0.54, 1.29)
≥ 1%	66 (88)	55 (61)	0.53 (0.37, 0.77)
≥ 5%	39 (54)	40 (43)	0.51 (0.32, 0.80)
≥ 10%	30 (43)	31 (34)	0.57 (0.34, 0.95)

In an exploratory post-hoc analysis using a non-validated assay, both tumour cell PD-L1 expression and tumour-associated immune cell (TAIC) PD-L1 expression were analysed in relation to the magnitude of treatment effect of nivolumab compared to investigator's choice. This analysis showed that not only tumour cell PD-L1 expression but also TAIC PD-L1 expression appeared to be associated with benefit from nivolumab relative to investigator's choice (see Table 21). Due to the small numbers of patients in the subgroups, and exploratory nature of the analysis, no definitive conclusions can be drawn from these data.

Table 21: Efficacy by tumour cell and TAIC PD-L1 expression (CA209141)

	Median OS[a] (months) HR[b] (95% CI)		Median PFS[a] (months) HR[b] (95% CI)		ORR (%) (95% CI)[c]	
	nivolumab	investigator's choice	nivolumab	investigator's choice	nivolumab	investigator's choice
PD-L1 ≥ 1%, PD-L1+ TAIC abundant[d] (61 nivolumab, 47 investigator's choice)	9.10	4.60	3.19	1.97	19.7	0
	0.43 (0.28, 0.67)		0.48 (0.31, 0.75)		(10.6, 31.8)	(0, 7.5)
PD-L1 ≥ 1%, PD-L1+ TAIC rare[d] (27 nivolumab, 14 investigator's choice)	6.67	4.93	1.99	2.04	11.1	7.1
	0.89 (0.44, 1.80)		0.93 (0.46, 1.88)		(2.4, 29.2)	(0.2, 33.9)
PD-L1 < 1%, PD-L1+ TAIC abundant[d] (43 nivolumab, 25 investigator's choice)	11.73	6.51	2.10	2.73	18.6	12.0
	0.67 (0.38, 1.18)		0.96 (0.55, 1.67)		(8.4, 33.4)	(2.5, 31.2)
PD-L1 < 1%, PD-L1+ TAIC rare[d] (27 nivolumab, 10 investigator's choice)	3.71	4.85	1.84	2.12	3.7	10.0
	1.09 (0.50, 2.36)		1.91 (0.84, 4.36)		(< 0.1, 19.0)	(0.3, 44.5)

[a] OS and PFS were estimated using Kaplan-Meier method.
[b] Hazard ratio in each subgroup derived from a Cox proportional hazards model with treatment as the only covariate.
[c] Confidence interval for ORR calculated using the Clopper-Pearson method.
[d] PD-L1+ TAIC in the tumour microenvironment were qualitatively assessed, and characterised as "numerous", "intermediate", and "rare" based on pathologist assessments. "Numerous" and "intermediate" groups were combined to define the "abundant" group.

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV (determined by p16 immunohistochemistry [IHC]). OS benefit was observed regardless of HPV status (HPV-positive: HR = 0.63; 95% CI: 0.38, 1.04, HPV-negative: HR = 0.64; 95% CI: 0.40, 1.03, and HPV-unknown: HR = 0.78; 95% CI: 0.55, 1.10).

Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, and 3-level EQ-5D. Over 15 weeks of follow-up, patients treated with nivolumab exhibited stable PROs, while those assigned to investigator's choice therapy exhibited significant declines in functioning (e.g., physical, role, social) and health status as well as increased symptomatology (e.g., fatigue, dyspnoea, appetite loss, pain, sensory problems, social contact problems). The PRO data should be interpreted in the context of the open-label study design and therefore taken cautiously.

Urothelial carcinoma

Treatment of advanced urothelial carcinoma

Intravenous formulation

Randomised open-label phase 3 study of nivolumab in combination with chemotherapy vs. chemotherapy (CA209901)

The safety and efficacy of nivolumab in combination with cisplatin and gemcitabine followed by nivolumab monotherapy were evaluated in a randomised open-label study CA209901 in cisplatin-eligible patients with unresectable or metastatic urothelial carcinoma. The study included subjects

(18 years or older) with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra, who were eligible for cisplatin and gemcitabine. Minor histologic variants (< 50% overall) were acceptable (TCC must have been the dominant histology). All subjects were required to have measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. No prior systemic anti-cancer therapy for metastatic or surgically unresectable urothelial carcinoma was permitted. Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place ≥ 12 months from completion of therapy. Prior intravesical therapy was permitted if completed at least 4 weeks prior to initiation of study treatment. Radiation therapy (with or without chemotherapy) with curative intent was permitted if treatment was completed ≥ 12 months before enrolment. Palliative radiotherapy was permitted as long as it was completed at least 2 weeks prior to therapy.

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n = 304) or cisplatin and gemcitabine (n = 304). Randomisation was stratified by tumour PD-L1 status (≥ 1% vs. < 1% or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥ 75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed at 1000 mg/m^2 IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m^2 IV over 30 to 120-minutes on Day 1 of the 3 week treatment cycle. A total of 92 patients (49 in the nivolumab in combination with cisplatin and gemcitabine arm and 43 in the cisplatin and gemcitabine arm) switched from cisplatin to carboplatin after at least one cycle of cisplatin.

The study demonstrated a statistically significant benefit in OS and PFS for patients randomised to nivolumab in combination with cisplatin and gemcitabine compared to cisplatin and gemcitabine alone. Efficacy results are presented in Table 22 and Figures 18 and 19.

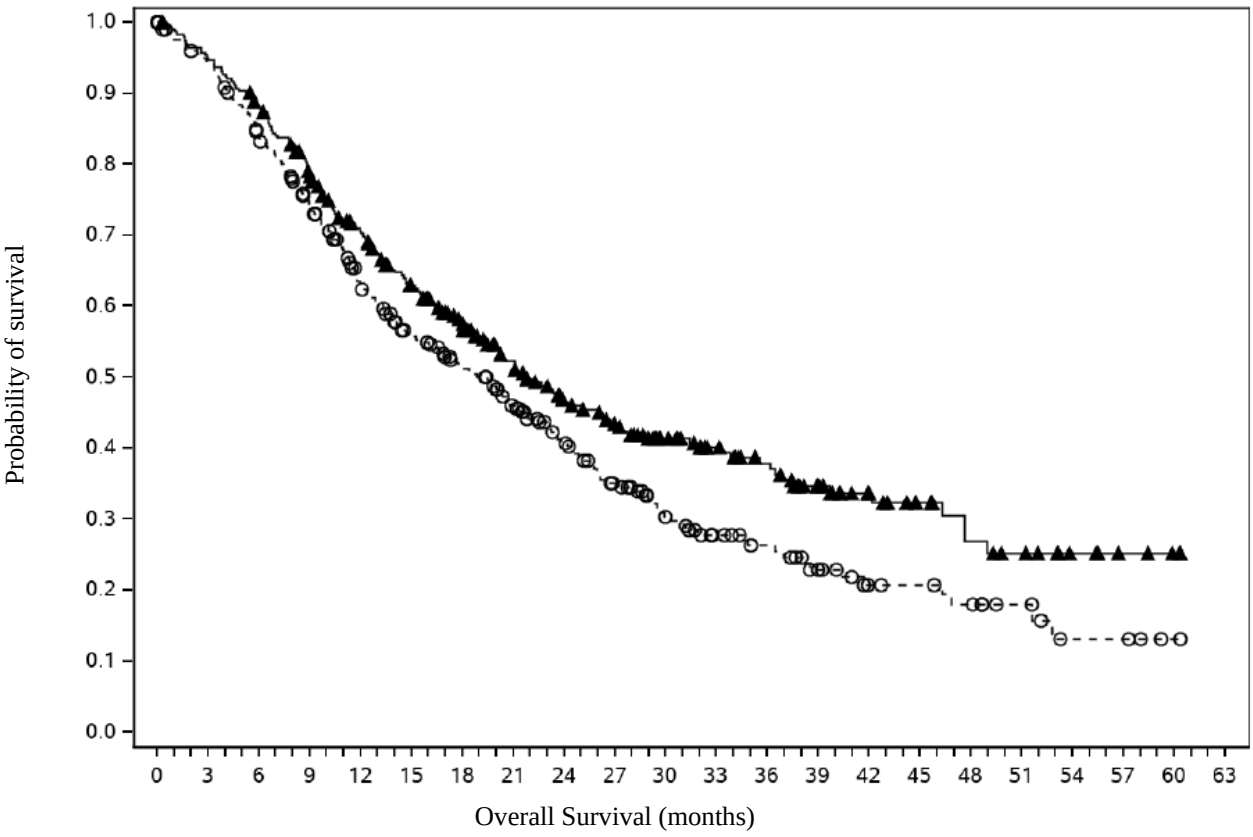
Table 22: Efficacy Results (CA209901)

	nivolumab and cisplatin-gemcitabine chemotherapy (n = 304)	**cisplatin- gemcitabine chemotherapy (n = 304)**
Overall Survival[a]		
Events	172 (56.6)	193 (63.5)
Median (months) (95% CI)	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival[a]		
Events	211 (69.4)	191 (62.8)
Median (months) (95% CI)	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)
Hazard ratio (95% CI)[b]	0.72 (0.59, 0.88)	
p-value[c]	0.0012	
Objective Response Rate		
Responders	175 (57.6)	131 (43.1)
(95% CI)	(51.8, 63.2)	(37.5, 48.9)

[a] Based on Kaplan-Meier Estimates

[b] Stratified Cox proportional hazard model.
[c] 2 sided p-value from stratified log-rank test.

Figure 18: Kaplan Meier curves of OS (CA209901)



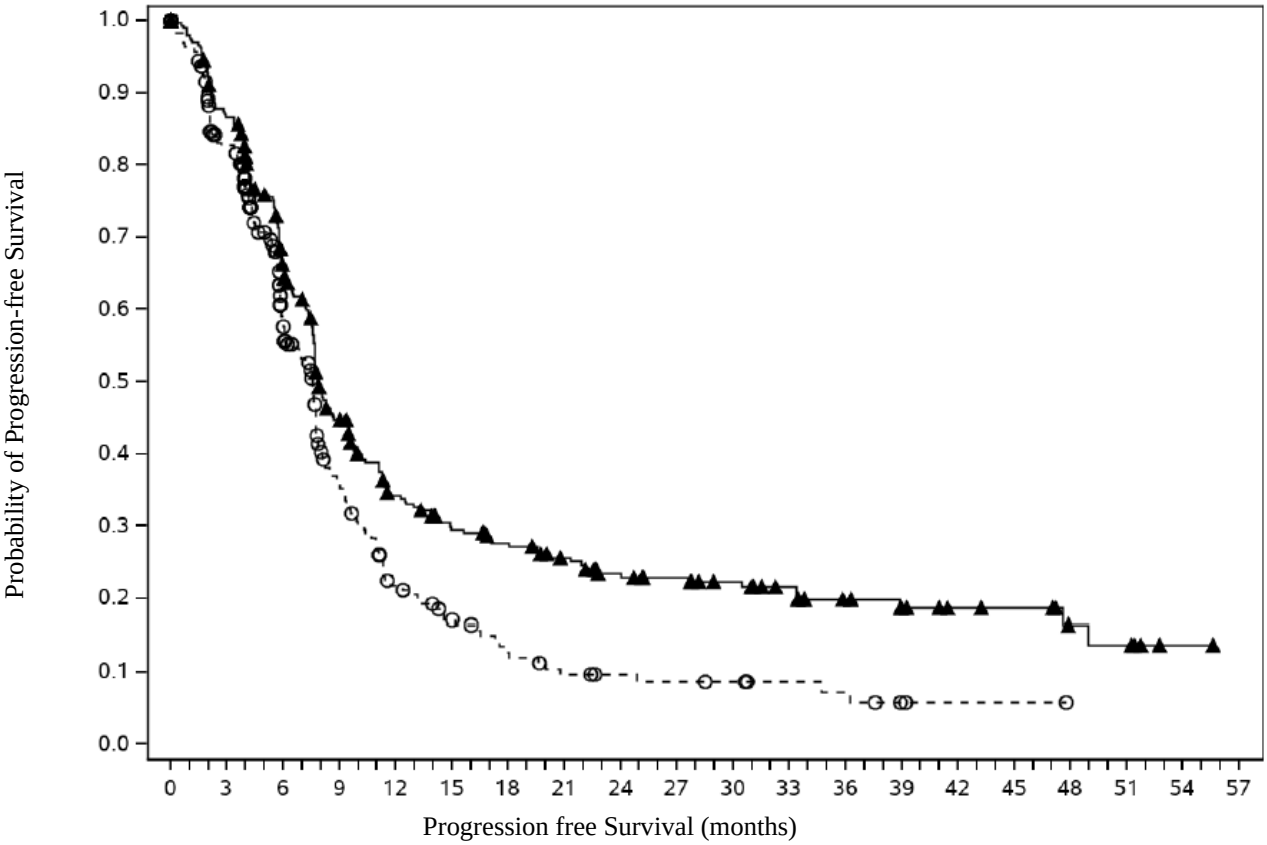
Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy																				
304	286	264	228	196	167	142	119	97	84	69	58	48	36	25	20	15	12	7	4	2	0
Gemcitabine-cisplatin chemotherapy																				
304	277	242	208	166	140	122	102	82	65	49	39	33	24	17	16	13	9	4	4	1	0

- - -▲- - - Nivolumab + gemcitabine-cisplatin chemotherapy (events: 172/304), median and 95% CI: 21.72 (18,63, 26.38)
- - -❍- - - Gemcitabine-cisplatin chemotherapy (events: 193/304), median and 95% CI: 18.85 (14.72, 22.44)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

Figure 19: Kaplan Meier curves of PFS (CA209901)



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy																				
304	253	179	116	82	65	57	49	41	36	31	26	19	14	11	10	10	6	5	1	0
Gemcitabine-cisplatin chemotherapy																				
304	223	119	63	35	25	17	12	12	10	9	8	6	5	2	1	1	0	0	0	0

- - -▲- - - Nivolumab + gemcitabine-cisplatin chemotherapy (events: 211/304), median and 95% CI: 7.92 (7.62, 9.49)

- - -❍- - - Gemcitabine-cisplatin chemotherapy (events: 191/304), median and 95% CI: 7.56 (6.05, 7.75)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

The primary analysis of PFS included censoring for new anti-cancer treatment before disease progression (Table 22). Results for PFS with and without censoring for new anti-cancer treatment before disease progression were consistent.

Intravenous formulation

Open-label phase 2 study (CA209275)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma was evaluated in a phase 2, multicentre, open-label, single-arm study (CA209275).

The study included patients (18 years or older) who had disease progression during or following platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients that received more than 2 prior lines of chemotherapy with liver metastases were excluded.

A total of 270 patients who received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks with a minimum follow-up of 8.3 months were evaluable for efficacy. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks thereafter up to 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit, did not have rapid disease progression, and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was ORR as determined by BICR. Additional efficacy measures included duration of response, PFS and OS.

The median age was 66 years (range: 38 to 90) with 55% ≥ 65 years of age and 14% ≥ 75 years of age. The majority of patients were white (86%) and male (78%). Baseline ECOG performance status was 0 (54%) or 1 (46%).

Table 23: Efficacy results (CA209275)[a]

	nivolumab (n = 270)
Confirmed objective response	54 (20.0%)
(95% CI)	(15.4, 25.3)
Complete response (CR)	8 (3.0%)
Partial response (PR)	46 (17.0%)
Stable disease (SD)	60 (22.2%)
Median duration of response[b]	
Months (range)	10.4 (1.9^{+}-12.0^{+})
Median time to response	
Months (range)	1.9 (1.6, 7.2)
Progression-free survival	
Events (%)	216 (80)
Median (95% CI) months	2.0 (1.9, 2.6)
Rate (95% CI) at 6 months	26.1 (20.9, 31.5)
Overall survival[c]	
Events (%)	154 (57)
Median (95% CI) months	8.6 (6.05, 11.27)
Rate (95% CI) at 12 months	41.0 (34.8, 47.1)

	Tumour PD-L1 expression level	
	< 1%	**≥ 1%**
Confirmed objective response (95% CI)		
	16% (10.3, 22.7) n = 146	25% (17.7, 33.6) n = 124
Median duration of response Months (range)		
	10.4 (3.7, 12.0^{+})	Not Reached (1.9^{+}, 12.0^{+})
Progression-free survival		
Median (95% CI) months	1.9 (1.8, 2.0)	3.6 (1.9, 3.7)
Rate (95% CI) at 6 months	22.0 (15.6, 29.2)	30.8 (22.7, 39.3)
Overall survival		
Median (95% CI) months	5.9 (4.37, 8.08)	11.6 (9.10, NE)
Rate (95% CI) at 12 months	34.0 (26.1, 42.1)	49.2 (39.6, 58.1)

"+" denotes a censored observation.

[a] median follow-up 11.5 months.

[b] Data unstable due to the limited duration of response.
[c] included 4 drug-related deaths: 1 pneumonitis, 1 acute respiratory failure, 1 respiratory failure, and 1 cardiovascular failure.
NE: non-estimable

Results from post-hoc, exploratory analyses indicate that in patients with low (e.g. < 1%) to no tumour PD-L1 expression, other patient characteristics (e.g. liver metastases, visceral metastases, baseline haemoglobin < 10g/dL and ECOG performance status = 1) might contribute to the clinical outcome.

Intravenous formulation

Open-label phase 1/2 study (CA209032)
CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients (including 18 subjects who received planned crossover treatment with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg combination) with similar inclusion criteria to study CA209275 treated with nivolumab monotherapy 3 mg/kg for urothelial carcinoma. At a minimum follow-up of 9 months, investigator-assessed confirmed ORR was 24.4% (95% CI: 15.3, 35.4). The median duration of response was not reached (range: 4.4-16.6^{+} months). The median OS was 9.7 months (95% CI: 7.26, 16.16) and the estimated OS rates were 69.2% (CI: 57.7, 78.2) at 6 months and 45.6% (CI: 34.2, 56.3) at 12 months.

Adjuvant treatment of urothelial carcinoma

Intravenous formulation

Randomised phase 3 study of adjuvant nivolumab vs. placebo (CA209274)
The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. The MIUC pathologic staging criteria that defines high risk patients was ypT2-ypT4a or ypN^{+} for adult patients who received neoadjuvant cisplatin chemotherapy, and pT3-pT4a or pN^{+} for adult patients who did not receive neoadjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. The study included patients regardless of their PD-L1 status, who had an ECOG performance status score of 0 or 1 (an ECOG PS of 2 was allowed for patients ineligible for neoadjuvant cisplatin chemotherapy). Tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. The study excluded patients with active, known or suspected autoimmune disease, patients who had treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

A total of 709 patients were randomised to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Of these, 282 patients had tumour cell PD-L1 expression ≥ 1%; 140 in the nivolumab arm and 142 in the placebo arm. Randomisation was stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression (≥ 1% vs. < 1%/indeterminate), and use of cisplatin neoadjuvant chemotherapy. Tumour imaging assessments were to be performed every 12 weeks from the date of first dose to week 96, then every 16 weeks from week 96 to week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years. The primary efficacy outcome measures were disease-free survival (DFS) in all randomised patients and DFS in randomised patients with tumour cell PD-L1 expression ≥ 1%. DFS was defined as the time between the date of randomisation and the date of the first documented recurrence assessed by investigator (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Secondary efficacy outcome measures included overall survival (OS).

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 66 years (range: 34-92 years), 76% were male and 76%

were white. Eighty two percent had muscle invasive bladder cancer (MIBC), 18% had upper tract urothelial carcinoma (UTUC) (renal pelvis and ureter), 42% of patients received prior cisplatin in the neoadjuvant setting, 45% of patients were N+ at radical resection, patients had ECOG performance status of 0 (61%), 1 (37%), or 2 (2%), and 7% of patients had a haemoglobin < 10 g/dL.

At the primary pre-specified interim analysis in patients with tumour cell PD-L1 expression ≥ 1% (minimum follow-up of 6.3 months and median follow-up of 22.1 months for the nivolumab arm), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab as compared to placebo. Median DFS as determined by the investigator was not reached (95% CI: 21.19, N.R.) for nivolumab versus 8.41 months (95% CI: 5.59, 21.19) for placebo, HR 0.55 (98.72% CI: 0.35, 0.85), p-value = 0.0005. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent.

In an updated descriptive DFS analysis in patients with tumour cell PD-L1 expression ≥ 1% (minimum follow-up of 11.4 months and median follow-up of 25.5 months for the nivolumab arm), DFS improvement was confirmed.

Efficacy results from this descriptive updated analysis are shown in Table 24 and Figure 20.

Table 24: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209274)

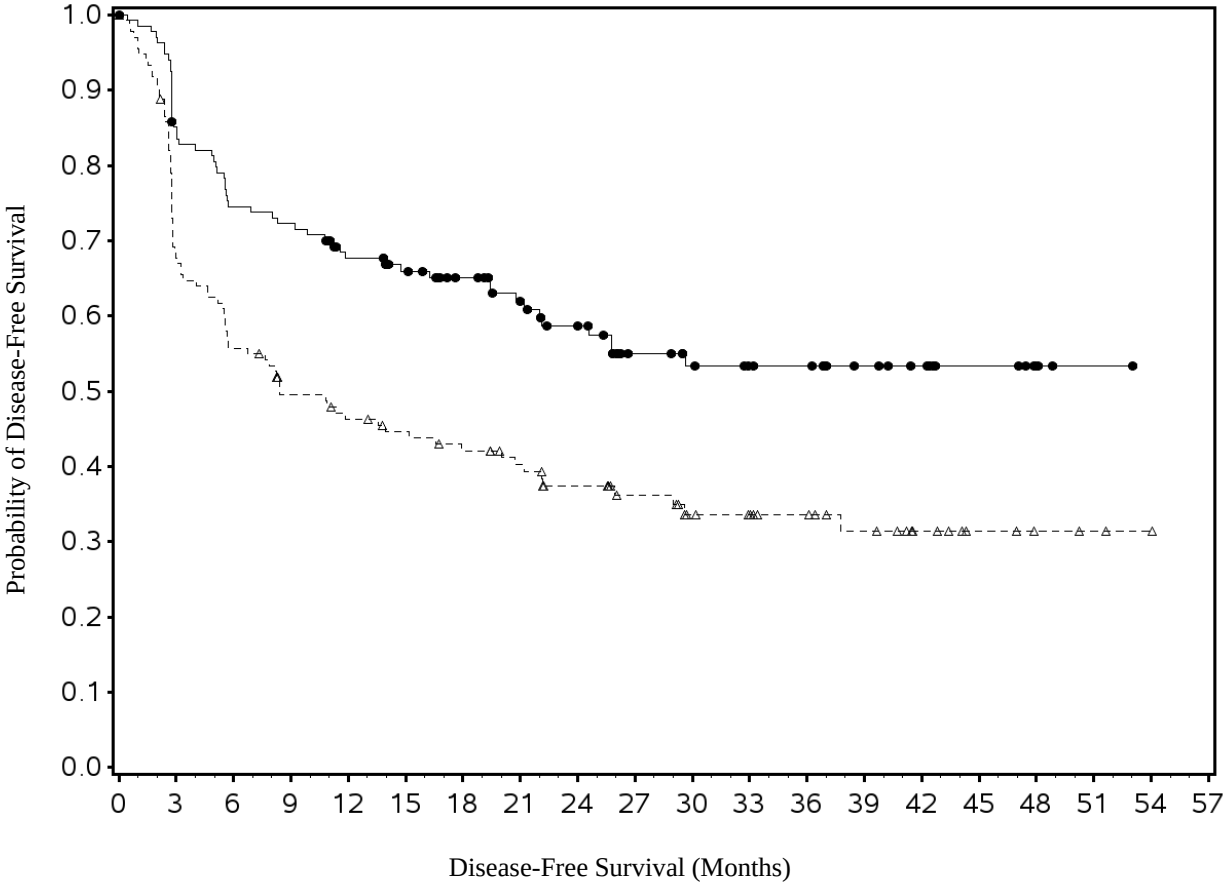
	nivolumab (n = 140)	**placebo** (n = 142)
Disease-Free Survival	Minimum follow-up 11.4 months	
Events (%)	56 (40.0)	85 (59.9)
Hazard ratio (95% CI)[a]	0.53 (0.38, 0.75)	
Median (95% CI) (months)[b]	NR (22.11, NE)	8.41 (5.59, 20.04)
Rate (95% CI) at 6 months	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)
Rate (95% CI) at 12 months	67.6 (59.0, 74.9)	46.3 (37.6, 54.5)
Rate (95% CI) at 24 months	58.6 (49.3, 66.9)	37.4 (29.0, 45.8)

NR: not reached, NE: non-estimable.

[a] Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.

[b] Based on Kaplan-Meier estimates.

Figure 20: Kaplan-Meier curves of DFS in patients with tumour cell PD-L1 expression ≥ 1% (CA209274)



Number of subjects at risk

Placebo																			
142	90	74	62	57	53	49	44	36	29	23	21	18	14	9	5	3	2	1	0
Nivolumab																			
140	113	99	96	85	75	67	58	50	38	33	30	29	22	19	8	3	1	0	0

- - -△- - - Placebo (events: 85/142), median and 95% CI: 8.41 (5.59, 20.04)
—●—— Nivolumab (events: 56/140), median and 95% CI: N.A. (22.11, N.A.)

Minimum follow-up of 11.4 months

Exploratory pre-specified subgroup descriptive analyses were performed in patients based on prior cisplatin treatment in the neoadjuvant setting.

In the subgroup of patients with tumour cell PD-L1 expression ≥ 1% who received prior cisplatin in the neoadjuvant setting (n = 118), the DFS HR was 0.37 (95% CI: 0.22, 0.64) with median DFS not reached and 8.41 months for the nivolumab and placebo arms, respectively. In the subgroup of patients with tumour cell PD-L1 expression ≥ 1% who did not receive prior cisplatin in the neoadjuvant setting (n = 164), the DFS HR was 0.69 (95% CI: 0.44, 1.08) with median DFS of 29.67 and 11.37 months for the nivolumab and placebo arms, respectively.

dMMR or MSI-H colorectal cancer

Intravenous formulation

Open-label study of nivolumab in combination with ipilimumab versus chemotherapy in dMMR or MSI-H CRC patients naive to treatment in the metastatic setting

The safety and efficacy of nivolumab 240 mg in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or metastatic CRC with known tumour MSI-H or dMMR status were

evaluated in a randomized, multi-arm, phase 3, open-label study (CA2098HW). Study treatment arms included nivolumab monotherapy, nivolumab in combination with ipilimumab, or investigator's choice of chemotherapy. MSI-H or dMMR tumour status was determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumour specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary efficacy population. Patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors were excluded from the study. Randomisation was stratified by tumour location (right vs left). Patients randomised to the chemotherapy arm could receive nivolumab plus ipilimumab combination upon progression assessed by BICR.

A total of 303 previously untreated patients, in the metastatic setting, were randomised to study, including 202 patients to nivolumab in combination with ipilimumab and 101 patients to chemotherapy. Among them 255 had centrally confirmed MSI-H/dMMR status, 171 in the nivolumab in combination with ipilimumab arm and 84 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 240 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the chemotherapy arm received: mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus followed by fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for nivolumab in combination with ipilimumab up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

The baseline characteristics of all randomised previously untreated for metastatic disease patients were: the median age was 63 years (range: 21 to 87), with 46% ≥ 65 years of age and 18% ≥ 75 years of age; 46% were male and 86% were White. Baseline ECOG performance status was 0 (54%) and ≥ 1 (46%); tumour location was right-sided or left-sided for 68% and 32% of patients, respectively; and 39 patients had confirmed Lynch syndrome among the 223 patients with a known status. The baseline characteristics of previously untreated for metastatic disease patients with centrally confirmed MSI-H/dMMR were consistent with all randomised previously untreated patients. Among the 101 patients randomised to receive chemotherapy, 88 received chemotherapy per protocol, including oxaliplatin-containing regimens (58%) and irinotecan-containing regimens (42%). Additionally, 66 patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

A primary efficacy outcome measure of the study was BICR-assessed PFS per RECIST 1.1. Additional efficacy measures included ORR assessed by BICR, OS, and duration of response.

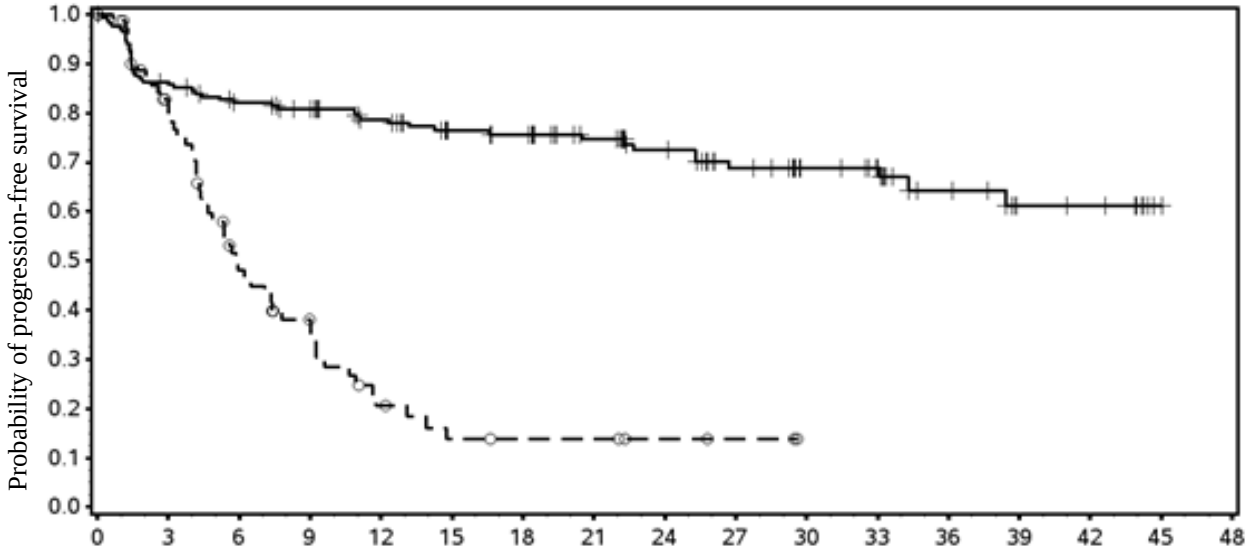
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 25 and Figure 21. At the time of this interim analysis, the other endpoints, including the data from nivolumab monotherapy arm, were not tested, due to testing hierarchy.

Table 25: Efficacy results in first-line MSI-H/dMMR centrally confirmed CRC (CA2098HW)[a,]

	nivolumab + ipilimumab (n = 171)	chemotherapy (n = 84)
Progression-free survival		
Events	48 (28%)	52 (62%)
Hazard ratio	0.21	
95% CI	(0.14, 0.32)	
p-value[b]	< 0.0001	
Median (95% CI) (months)	NR (38.4, NR)	5.9 (4.4, 7.8)

[a] Median follow-up of 31.5 months (range: 6.1 to 48.4 months).
[b] Based on stratified 2-sided log-rank test.

Figure 21: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Number of subjects at risk

Nivolumab + ipilimumab																
171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Investigator's choice																
84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

—O—— Nivolumab + ipilimumab (events: 48/171), median and 95% CI: N.A. (38.44, N.A.)
- - -+- - - Chemotherapy (events: 52/84), median and 95% CI: 5.85 (4.37, 7.79)

Open-label study of nivolumab in combination with ipilimumab in dMMR or MSI-H CRC in patients who received prior fluoropyrimidine-based combination chemotherapy

The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of dMMR or MSI-H metastatic CRC was evaluated in a Phase 2, multi-centre, open-label, single-arm study (CA209142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan. Patients who had their most recent prior treatment in the adjuvant setting should have progressed on or within 6 months of completion of adjuvant chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1

status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients were treated with nivolumab 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary outcome measure was investigator-assessed ORR. Secondary outcome measures were BICR-assessed ORR and disease control rate. Analysis of ORR included duration of and time to response. Exploratory outcome measures included PFS and OS.

The median age was 58 years (range: 21-88) with 32% ≥ 65 years of age and 9% ≥ 75 years of age, 59% were male and 92% were white. Baseline ECOG performance status was 0 (45%) or 1 (55%), 25% of patients had BRAF mutations, 37% had KRAS mutations, and 12% were unknown. Of the 119 treated patients, 109 had received prior fluoropyrimidine based chemotherapy in the metastatic setting and 9 in the adjuvant setting. Before study enrolment, of the 119 treated patients, 118 (99%) had received fluorouracil, 111 (93%) had received oxaliplatin, 87 (73%) had received irinotecan as part of prior therapies; 82 (69%) had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Twenty three percent, 36%, 24%, and 16% received 1, 2, 3, or 4 or more prior therapies respectively, and 29% of patients had received an EGFR inhibitor.

Efficacy results (minimum follow-up 46.9 months; median follow-up 51.1 months) are shown in Table 26.

Table 26: Efficacy results (CA209142)*

	nivolumab + ipilimumab (n = 119)
Confirmed objective response, n (%)	77 (64.7)
(95% CI)	(55.4, 73.2)
Complete response (CR), n (%)	15 (12.6)
Partial response (PR), n (%)	62 (52.1)
Stable disease (SD), n (%)	25 (21.0)
Duration of response	
Median (range) months	NR (1.4, 58.0+)
Median time to response	
Months (range)	2.8 (1.1, 37.1)

* per investigator assessment
"+" denotes a censored observation.
NR = not reached

The BICR-assessed ORR was 61.3% (95% CI: 52.0, 70.1), including CR rate of 20.2% (95% CI: 13.4, 28.5), PR rate of 41.2% (95% CI: 32.2, 50.6) and stable disease reported in 22.7%. BICR assessments were generally consistent with the investigator assessment. Confirmed responses were observed regardless of BRAF or KRAS mutation status, and tumour PD-L1 expression levels.

Of 119 patients 11 (9.2%) patients were ≥ 75 years. The investigator assessed ORR in patients ≥ 75 years was 45.5% (95% CI: 16.7, 76.6).

Oesophageal squamous cell carcinoma

Intravenous formulation

Randomised phase 3 study of nivolumab monotherapy in previously treated patients (ONO-4538-24/ CA209473)

The safety and efficacy of nivolumab 240 mg monotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) was evaluated in a phase 3 randomised active-controlled, open-label study (ONO-4538-24/CA209473). The study included adult patients (20 years or older) who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based combination regimen, and patients were enrolled regardless of tumour PD-L1 expression level. Patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had active autoimmune disease, medical conditions requiring systemic immunosuppression, and patients with apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), were excluded from the study.

A total of 419 patients were randomised 1:1 to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n = 210) or investigator's choice of taxane chemotherapy: either docetaxel (n = 65) 75 mg/m^2 intravenously every 3 weeks, or paclitaxel (n = 144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off. Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases (≤ 1 vs. ≥ 2) and tumour PD-L1 expression (≥ 1% vs. <1% or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 65 years (range: 33-87), 53% were ≥ 65 years of age, 10% were aged ≥ 75 years, 87% were male, 96% were Asian and 4% were white. Baseline ECOG performance status was 0 (50%) or 1 (50%).

With a minimum follow-up of 17.6 months, the study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice taxane chemotherapy. Efficacy results are shown in Table 27 and Figure 22.

A higher proportion of patients experienced death within the first 2.5 months in the nivolumab arm (32/210, 15.2%) as compared to the chemotherapy arm (15/209, 7.2%). No specific factor(s) associated with early deaths could be identified.

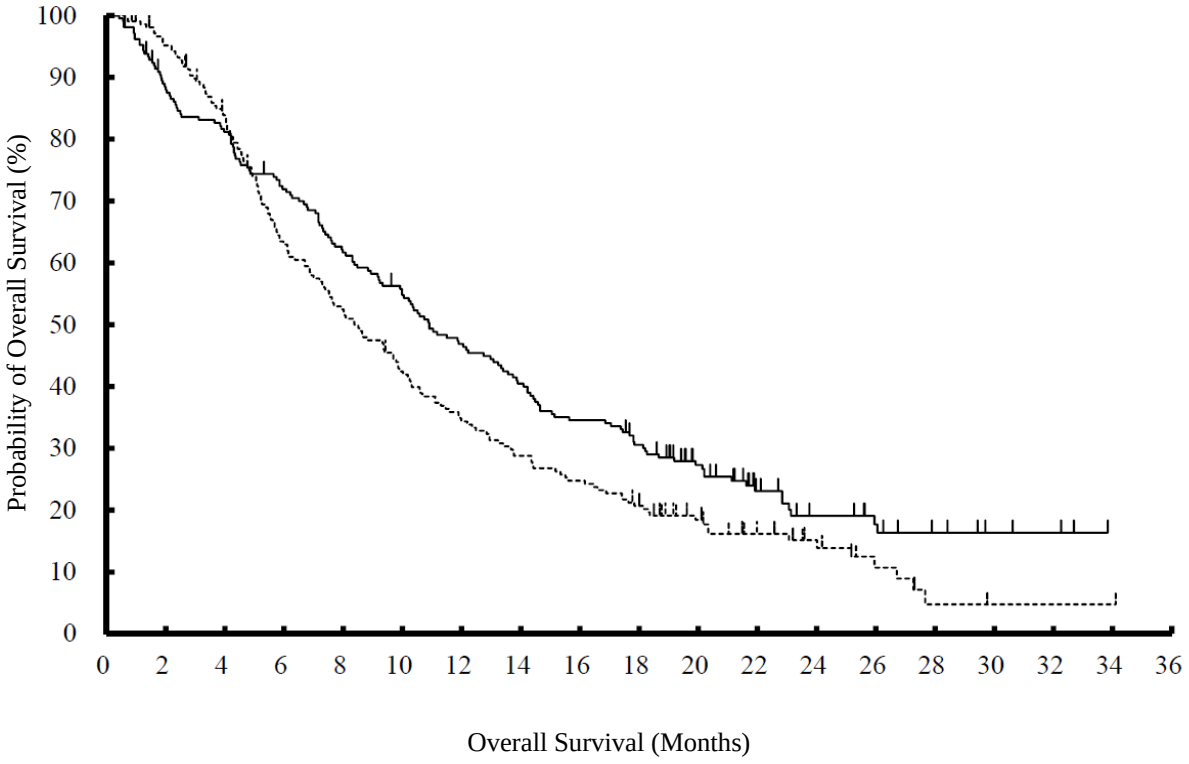
Table 27: Efficacy results (ONO-4538-24/CA209473)

	nivolumab (n = 210)	**investigator's choice (n = 209)**
Overall Survival[a]		
Events	160 (76%)	173 (83%)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Median (95% CI) (months)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)

	nivolumab (n = 210)	investigator's choice (n = 209)
Objective Response Rate[d, e]	33 (19.3%)	34 (21.5%)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response	1 (0.6%)	2 (1.3%)
Partial response	32 (18.7%)	32 (20.3%)
Stable disease	31 (18.1%)	65 (41.1%)
Median duration of response (95% CI) (months)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
Progression-Free Survival[a]		
Events	187 (89%)	176 (84%)
Median (95% CI) (months)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	

[a] Based on ITT analysis.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] Based on Response Evaluable Set (RES) analysis, n = 171 in nivolumab group and n = 158 in investigator's choice group.
[e] Not significant, p-value 0.6323.

Figure 22: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)



Number of subjects at risk

Nivolumab

210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0

Investigator's choice

209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

———— Nivolumab - - - - - - Investigator's choice

Of the 419 patients, 48% had tumour PD-L1 expression ≥ 1%. The remaining 52% of patients had tumour PD-L1 expression <1%. The hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the nivolumab and investigator's choice taxane chemotherapy arms, respectively, in the tumour PD-L1 positive subgroup. In the tumour PD-L1

negative OSCC subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the nivolumab and chemotherapy arms, respectively.

Intravenous formulation

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy and nivolumab in combination with chemotherapy vs. chemotherapy as first-line treatment (CA209648)
The safety and efficacy of nivolumab in combination with ipilimumab and nivolumab in combination with chemotherapy were evaluated in a randomised, active-controlled, open-label study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic OSCC. Patients were enrolled regardless of their tumour PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of oesophagus, not amenable to chemoradiation and/or surgery. Prior adjuvant, neoadjuvant, or definitive chemotherapy, radiotherapy or chemoradiotherapy was permitted if given as part of curative intent regimen prior to trial enrollment. Patients who had a baseline performance score ≥ 2, had brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the study. Randomisation was stratified by tumour cell PD-L1 status (≥ 1% vs. < 1% or indeterminate), region (East Asia vs. rest of Asia vs. rest of world), ECOG performance status (0 vs. 1), and number of organs with metastases (≤ 1 vs. ≥ 2).

A total of 970 patients were randomised to receive either nivolumab in combination with ipilimumab, (n = 325), nivolumab in combination with chemotherapy (n = 321) or chemotherapy (n = 324). Of these, 473 patients had tumour cell PD-L1 expression ≥ 1%,158 in the nivolumab plus ipilimumab arm, 158 in the nivolumab plus chemotherapy arm, and 157 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks, and patients in the nivolumab plus chemotherapy arm received nivolumab 240 mg every 2 weeks on days 1 and 15, fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Patients in the chemotherapy arm received fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Treatment continued until disease progression, unacceptable toxicity, or up to 24 months. Patients in the nivolumab plus ipilimumab arm who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Patients in the nivolumab plus chemotherapy arm in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued.

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 63 years (range: 26-85), 8.2% were ≥ 75 years of age, 81.8% were male, 73.1% were Asian, and 23.3% were white. Patients had histological confirmation of squamous cell carcinoma (98.9%) or adenosquamous cell carcinoma (1.1%) in the oesophagus. Baseline ECOG performance status was 0 (45.2%) or 1 (54.8%).

Nivolumab in combination with chemotherapy vs. chemotherapy
The primary efficacy outcome measures were PFS (by BICR) and OS in patients with tumour cell PD-L1 expression ≥ 1%. Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 12.9 months the study demonstrated a statistically significant improvement in OS and PFS in patients with tumour cell PD-L1 expression ≥ 1%. Efficacy results are shown in Table 28.

Table 28: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

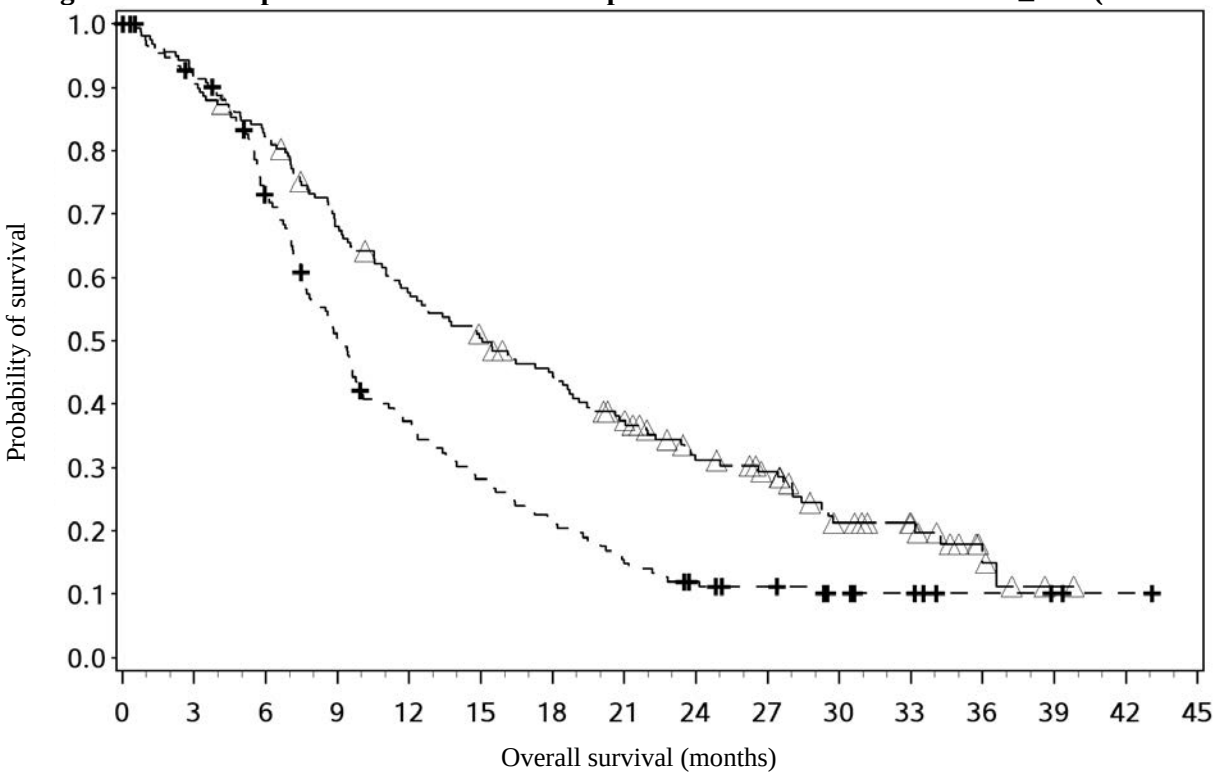
	nivolumab + chemotherapy (n = 158)	chemotherapy[a] (n = 157)
Overall survival		
Events	98 (62.0%)	121 (77.1%)
Hazard ratio (99.5% CI)[b]	0.54 (0.37, 0.80)	
p-value[c]	< 0.0001	
Median (95% CI) (months)[d]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	58.0 (49.8, 65.3)	37.1 (29.2, 44.9)
Progression-free survival[e]		
Events	117 (74.1%)	100 (63.7%)
Hazard ratio (98.5% CI)[b]	0.65 (0.46, 0.92)	
p-value[c]	0.0023	
Median (95% CI) (months)[d]	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months[d]	25.4 (18.2, 33.2)	10.5 (4.7, 18.8)
Overall response rate, n (%)[e]	84 (53.2)	31 (19.7)
(95% CI)	(45.1, 61.1)	(13.8, 26.8)
Complete response	26 (16.5)	8 (5.1)
Partial response	58 (36.7)	23 (14.6)
Duration of response[e]		
Median (95% CI) (months)[d]	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)
Range	1.4^{+}, 34.6	1.4^{+}, 31.8^{+}

[a] Fluorouracil and cisplatin.
[b] Based on stratified Cox proportional hazard model.
[c] Based on stratified 2-sided log-rank test.
[d] Based on Kaplan-Meier estimates.
[e] Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 15.05 months (95% CI: 11.93, 18.63) for nivolumab plus chemotherapy vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.59; 95% CI: 0.46, 0.76). Median PFS was 6.93 months (95% CI: 5.68, 8.35) for nivolumab plus chemotherapy vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 0.66; 95% CI: 0.50, 0.87). The ORR was 53.2% (95% CI: 45.1, 61.1) for nivolumab plus chemotherapy vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.

The Kaplan-Meier curves for OS and PFS with a minimum follow-up of 20 months are shown in Figures 23 and 24.

Figure 23: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



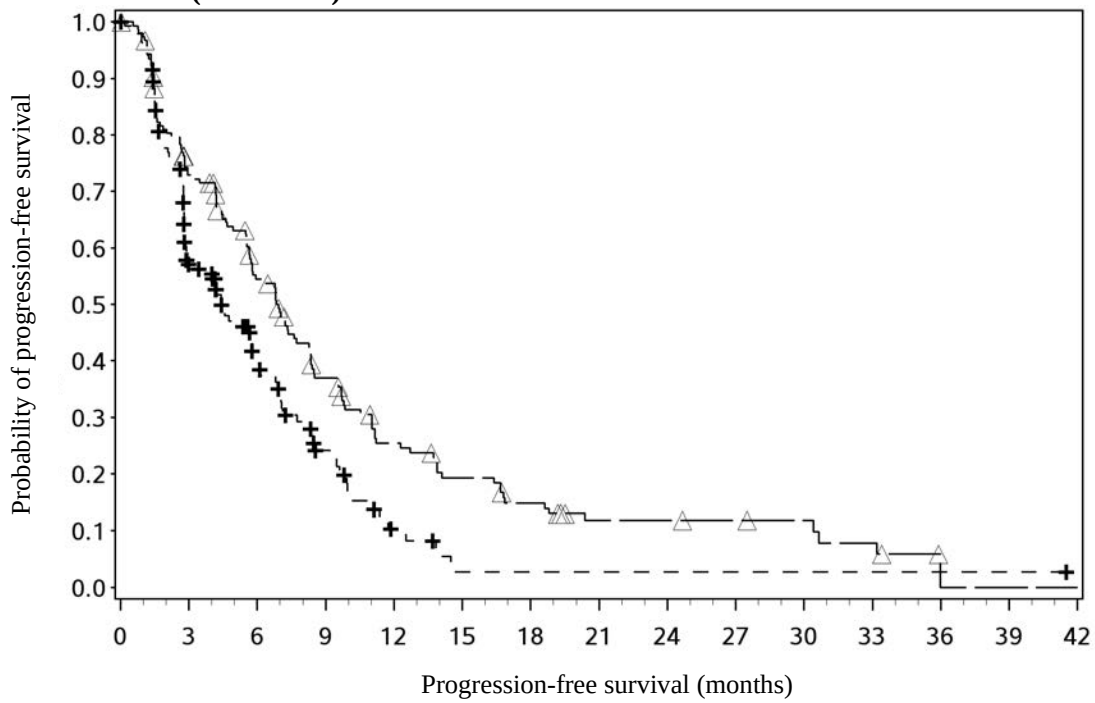
Number of subjects at risk

Nivolumab + chemotherapy															
158	143	129	105	88	76	66	52	38	32	19	15	5	1	0	0
Chemotherapy															
157	137	107	73	53	40	30	21	15	12	8	6	3	2	1	0

- - -△- - - Nivolumab + chemotherapy (events: 118/158), median and 95% CI: 15.05 (11.93, 18.63)
- - -+- - - Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Figure 24: Kaplan-Meier curves of PFS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



Number of subjects at risk

Nivolumab + chemotherapy														
158	107	75	47	30	22	16	10	10	7	6	4	0	0	0
Chemotherapy														
157	68	36	17	5	1	1	1	1	1	1	1	1	1	0

- - -△- - - Nivolumab + chemotherapy (events: 123/158), median and 95% CI: 6.93 (5.65, 8.35)
- - -+- - - Chemotherapy (events: 101/157), median and 95% CI: 4.44 (2.89, 5.82)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer

Intravenous formulation

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209577). The study included adult patients who had received CRT, followed by complete surgical resection of carcinoma within 16 weeks prior to randomisation, and who had residual pathologic disease as confirmed by the investigator, with at least ypN1 or ypT1. Patients with a baseline performance score ≥ 2, who did not receive concurrent CRT prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were enrolled regardless of tumour PD-L1 expression level.

A total of 794 patients were randomised 2:1 to receive either nivolumab 240 mg (n = 532) or placebo (n = 262). Patients were administered nivolumab intravenously over 30 minutes every 2 weeks for 16 weeks followed by 480 mg infused over 30 minutes every 4 weeks beginning at week 17. Patients were administered placebo over 30 minutes with the same dosing schedule as nivolumab. Randomisation was stratified by tumour PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). Treatment continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. The primary efficacy outcome measure was disease-free survival (DFS), as assessed by the investigator, defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant from the primary resected site) or death from any

cause, whichever occurred first. Patients on treatment underwent imaging for tumour recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 26-86) with 36% ≥ 65 years of age and 5% ≥ 75 years of years. The majority of patients were white (82%) and male (85 %). Baseline ECOG performance status was 0 (58%) or 1 (42%).

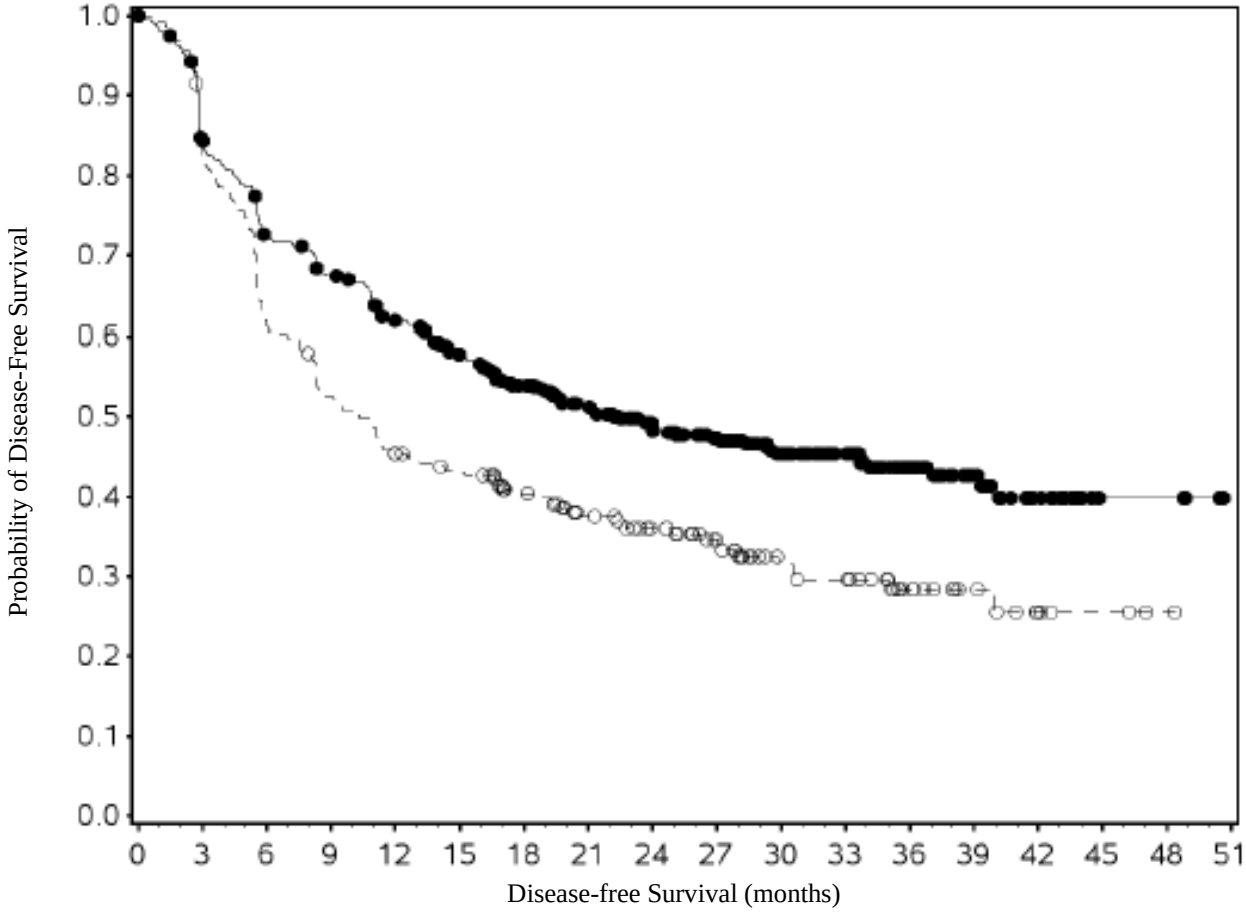
At the primary pre-specified interim analysis (minimum of 6.2 months and a median of 24.4 months follow-up), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab compared with placebo. Median DFS as determined by the investigator was 22.41 months (95% CI: 16.62, 34.00) for nivolumab versus 11.04 months (95% CI: 8.34, 14.32) for placebo, HR 0.69 (96.4% CI: 0.56, 0.86), p-value < 0.0003. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent. In an updated descriptive DFS analysis with minimum of 14 months and median of 32.2 months follow-up, DFS improvement was confirmed. Efficacy results from this descriptive secondary analysis are shown in Table 29 and Figure 25.

Table 29: Efficacy results (CA209577)

	nivolumab (n = 532)	**placebo (n = 262)**
Disease-free Survival[a] with minimum follow-up 14 months[c]		
Events (%)	268 (50)	171 (65)
Hazard ratio (95% CI)[b]	0.67 (0.55, 0.81)	
Median (95% CI) (months)	22.4 (17.0, 33.6)	10.4 (8.3, 13.9)
Rate (95% CI) at 6 months	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)
Rate (95% CI) at 12 months	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
Rate (95% CI) at 24 months	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)

[a] Based on all randomised patients.
[b] Based on a stratified cox proportional hazards model.
[c] Descriptive analysis based on data cut-off: 18-Feb-2021.

Figure 25: Kaplan-Meier curves of DFS (CA209577)



Number of subjects at risk

Nivolumab																	
532	433	371	342	307	272	228	194	160	137	106	84	57	34	19	4	4	0
Placebo																	
262	211	158	134	114	107	88	73	62	50	33	30	18	11	5	3	1	0

—●— Nivolumab (events: 268/532), median and 95% CI: 22.41 (16.95, 33.64)
- - -○- - - Placebo (events: 171/262), median and 95% CI: 10.35 (8.31, 13.93)
Based on data cut-off: 18-Feb-2021, minimum follow-up of 14 months

DFS benefit was observed regardless of histology and PD-L1 expression.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

Intravenous formulation
The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy (dose and schedule of nivolumab selected depending on the chemotherapy regimen used, see below) was evaluated in a phase 3, randomised, open-label study (CA209649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. Patients were enrolled regardless of their tumour cell PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. A retrospective re-scoring of a patient's tumour PD-L1 status using CPS was conducted using the PD-L1-stained tumour specimens used for randomisation. Patients with known HER2-positive tumours, who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, or who had active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. A total of 643 patients with HER2-undetermined status (40.3% of the study population) were included in the study. Randomisation was stratified by tumour cell PD-L1 status (≥ 1% vs. < 1% or indeterminate),

region (Asia vs. US vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy regimen. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy or chemotherapy. Of these, 955 patients had PD-L1 CPS ≥ 5; 473 in the nivolumab plus chemotherapy arm and 482 in the chemotherapy arm. Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 intravenously on day 1 and fluorouracil 1200 mg/m^2 intravenously by continuous infusion over 24 hours daily or per local standard on days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m^2 intravenously on day 1 and capecitabine 1000 mg/m^2 orally twice daily on days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks up to 24 months after treatment initiation. Tumour assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

Baseline characteristics were generally balanced across treatment groups. In patients with PD-L1 CPS ≥ 5, the median age was 62 years (range: 18-90), 11% were ≥ 75 years of age, 71% were male, 25% were Asian and 69% were white. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumour locations were distributed as gastric (70%), GEJ (18%) and oesophagus (12%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 CPS ≥ 5 based on the PD-L1 IHC 28-8 pharmDX. Secondary endpoints per the pre-specified hierarchical testing were OS in patients with PD-L1 CPS ≥ 1 and in all randomised patients; further endpoints included ORR (BICR) in PD-L1 CPS ≥ 5 and all randomised patients. At the primary pre-specified analysis, with a minimum follow-up of 12.1 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with PD-L1 CPS ≥ 5. Median OS was 14.4 months (95% CI: 13.1, 16.2) for nivolumab in combination with chemotherapy vs. 11.1 months (95% CI: 10.0, 12.1) for chemotherapy (HR = 0.71; 98.4% CI: 0.59, 0.86; p-value <0.0001). Median PFS was 7.69 months (95% CI: 7.03, 9.17) for nivolumab in combination with chemotherapy vs. 6.05 months (95% CI: 5.55, 6.90) for chemotherapy (HR = 0.68; 98% CI: 0.56, 0.81; p-value <0.0001). The ORR was 60% (95% CI: 55, 65) for nivolumab in combination with chemotherapy vs. 45% (95% CI: 40, 50) for chemotherapy.

At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 30, and Figures 26 and 27.

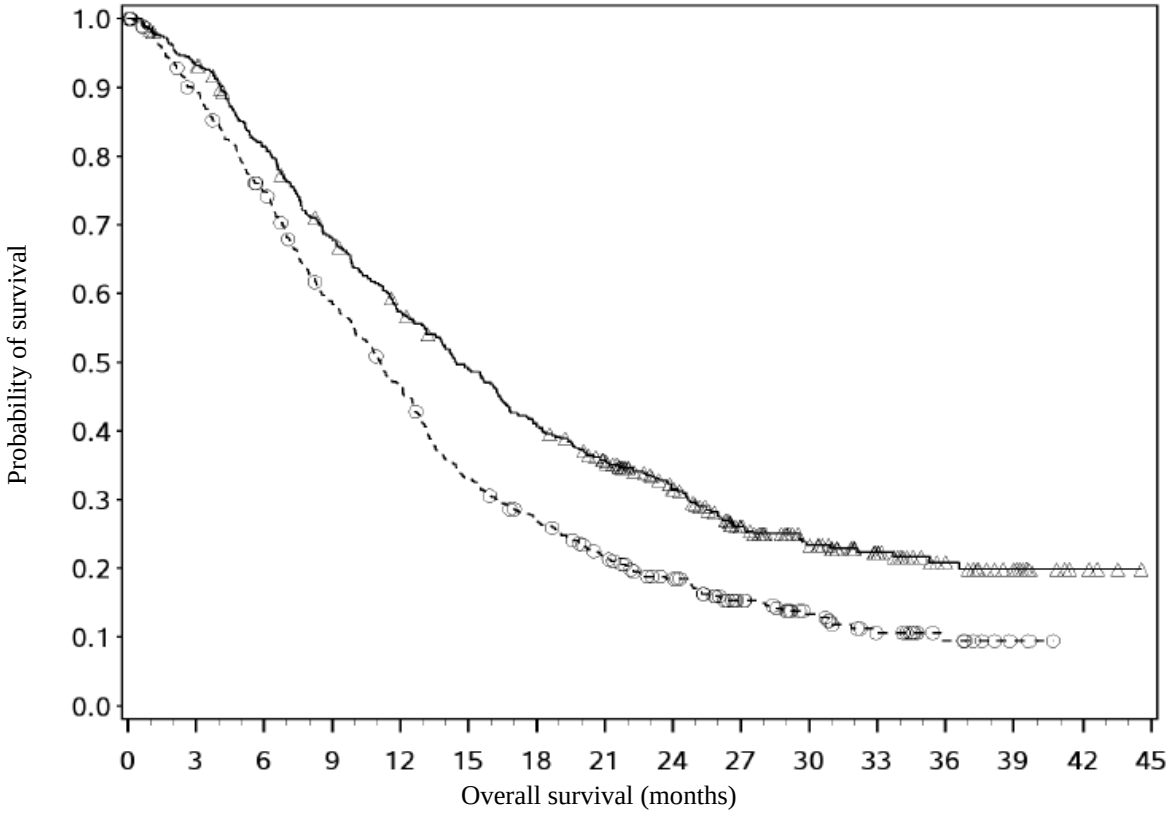
Table 30: Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

	nivolumab + chemotherapy (n = 473)	**chemotherapy (n = 482)**
	Minimum follow-up 19.4 months[a]	
Overall survival		
Events	344 (73%)	397 (82%)
Hazard ratio (95% CI)[b]	0.69 (0.60, 0.81)	
Median (95% CI) (months)[c]	14.4 (13.1, 16.3)	11.1 (10.0, 12.1)
Rate (95% CI) at 12 months	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)
Progression-free survival[d]		
Events	342 (72.3%)	366 (75.9%)
Hazard ratio (95% CI)[b]	0.68 (0.59, 0.79)	
Median (95% CI) (months)[c]	8.31 (7.03, 9.26)	6.05 (5.55, 6.90)
Rate (95% CI) at 12 months	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Objective response rate, n[d,e]	227/378 (60%)	176/390 (45%)
(95% CI)	(54.9, 65.0)	(40.1, 50.2)
Complete response	12.2%	6.7%
Partial response	47.9%	38.5%
Duration of response[d,e]		
Median (95% CI) (months)[c]	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)

[a] Descriptive analysis based on data cut-off: 04-Jan-2021.
[b] Based on stratified long Cox proportional hazard model.
[c] Kaplan-Meier estimate.
[d] Confirmed by BICR.
[e] Based on patients with measurable disease at baseline.

Figure 26: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)

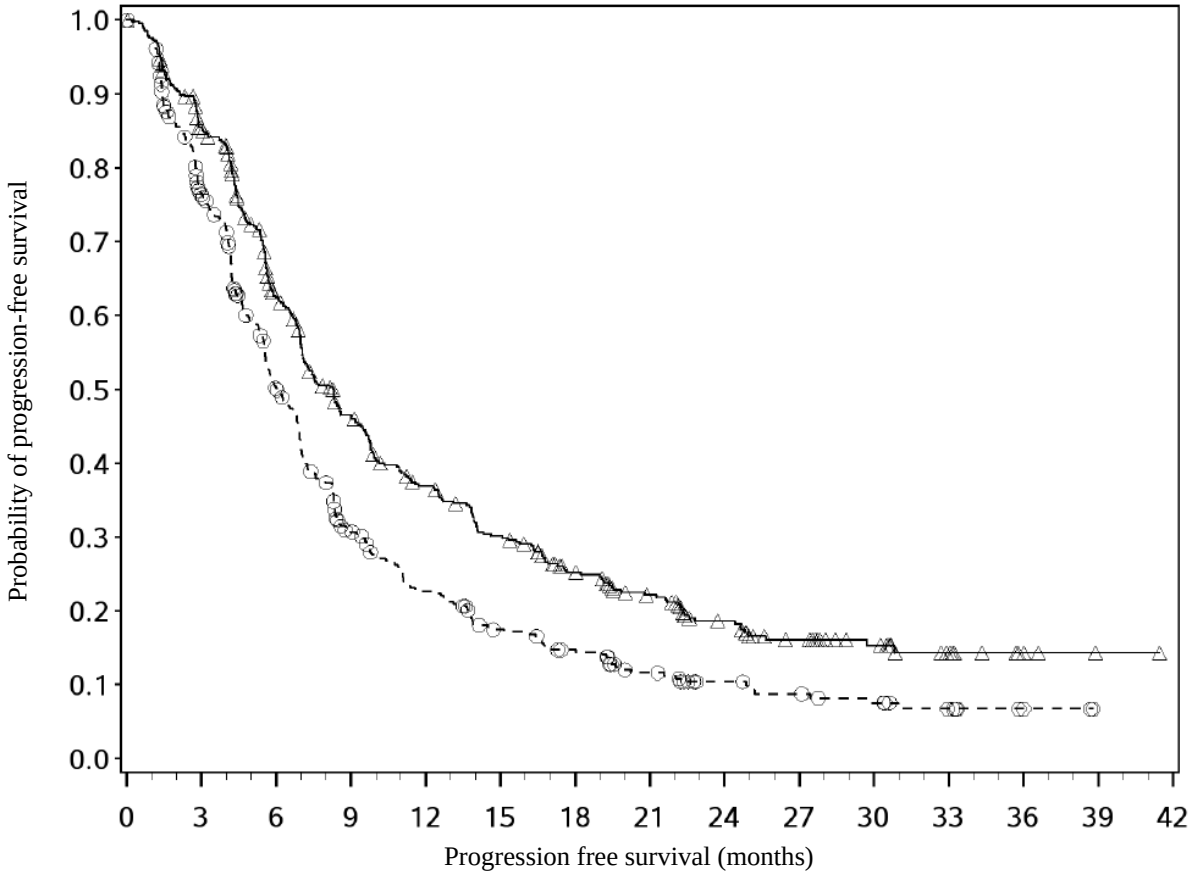


Number of subjects at risk

Nivolumab + chemotherapy															
473	439	378	314	263	223	187	155	118	78	56	37	23	13	4	0
Chemotherapy															
482	421	350	272	213	152	122	92	68	44	28	16	8	2	0	0

—△—— Nivolumab + chemotherapy (events: 344/473), median and 95% CI: 14.42 (13.14, 16.26)
- - -❍- - - Chemotherapy (events: 397/482), median and 95% CI: 11.10 (10.02, 12.09)
Minimum follow-up of 19.4 months

Figure 27: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥ 5 (CA209649)



Number of subjects at risk

Nivolumab + chemotherapy														
473	386	259	186	143	115	88	67	47	31	20	11	4	1	0
Chemotherapy														
482	328	202	114	81	58	46	30	20	16	12	7	3	0	0

—△—— Nivolumab + chemotherapy (events: 342/473), median and 95% CI: 8.31 (7.03, 9.26)
- - -❍- - - Chemotherapy (events: 397/482), median and 95% CI: 6.05 (5.55, 6.90)
Minimum follow-up of 19.4 months

Paediatric population

Subcutaneous formulation
No dedicated studies of OPDIVO solution for injection have been conducted in paediatric patients.

The European Medicines Agency has waived the obligation to submit the results of studies with OPDIVO solution for injection for subcutaneous use in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system neoplasms, haematopoietic and lymphoid tissue neoplasms other than Hodgkin lymphoma) (see section 4.2 for information on paediatric use).

Safety and efficacy in elderly patients

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population.

5.2 Pharmacokinetic properties

Nivolumab solution for injection pharmacokinetics (PK) were assessed using a population PK approach. The PK was studied at a dose of 1200 mg administered as multiple doses every 4 weeks.

Nivolumab time-averaged serum concentration over 28 days (Cavgd28) showed non-inferiority of subcutaneous nivolumab (77.4 mcg/mL) to intravenous nivolumab (36.9 mcg/mL), with a geometric mean ratio of 2.098 (90% CI: 2.001, 2.200). Nivolumab minimum serum concentration at steady state (C_{minss}) showed non-inferiority of subcutaneous nivolumab (122.2 mcg/mL) to intravenous nivolumab (68.9 mcg/mL), with a geometric mean ratio of 1.774 (90% CI: 1.633, 1.927).

Absorption

The mean absorption rate constant (Ka) and bioavailability (F) of nivolumab solution for injection are 0.0123 hr-1 (or 0.295 Day-1) and 78.8%, respectively. Peak concentrations occurred by around 6 days.

Distribution

The geometric mean (CV%) volume of distribution at steady state (Vss) is 6.32 L (21.3%).

Elimination

Nivolumab solution for injection human clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.6% (15.8%) resulting in a geometric mean (CV%) steady-state clearance (CLss) of 7.18 mL/h (52.3%) in patients with RCC; the decrease in CLss is not considered clinically relevant.

The geometric mean (CV%) elimination half-life (t1/2) is 26.5 days (32.1%).

Special populations

The following factors had no clinically important effect on the bioavailability of nivolumab solution for injection: sex and performance status. The following factors had no clinically important effect on the clearance of nivolumab solution for injection: body weight (35 to 153 kg), sex, eGFR (24 to 124 mL/min/1.73 m^2), or performance status.

Renal impairment
In population PK analyses for intravenous nivolumab, the effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 m^2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m^2; n = 342). No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 4.2).

Hepatic impairment
In population PK analyses for intravenous nivolumab, the effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804). No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, foetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response and immune-related disorders have been reported in PD-1 knockout mice.

Fertility studies have not been performed with nivolumab.

Subcutaneous formulation

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 revealed embryofoetal toxicity in mice at high systemic exposure but did not show teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
Histidine
Histidine hydrochloride monohydrate
Sucrose
Pentetic acid
Polysorbate 80 (E433)
Methionine
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years

Storage in syringe

From a microbiological point of view, once transferred from the vial to the syringe, the medicinal product should be used immediately since the medicinal product does not contain any antimicrobial preservative or bacteriostatic agents. If not used immediately, OPDIVO solution for injection

transferred to the syringe can be stored in the refrigerator at 2°C to 8°C, protected from light for up to 7 days and/or at room temperature 20°C to 25°C and room light for up to 8 hours. Discard if storage time exceeds these limits. Aseptic handling should be ensured during the preparation of the syringe for injection.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after preparation of the syringe, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper and an aluminium seal with a plastic orange flip-off cap containing 5 mL of solution for injection.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Preparation of the syringe

OPDIVO solution for injection is for single use only and is ready to use.

OPDIVO solution for injection should NOT be diluted or mixed with other medicinal products.

OPDIVO solution for injection is compatible with polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride, fluorinated ethylene propylene, and stainless steel.

OPDIVO solution for injection should be a clear to opalescent, colourless to yellow solution. Prior to use, visually inspect and discard if discoloured or contains extraneous particulate matter other than a few translucent-to-white particles.

Do not shake the vial.

A syringe and a transfer needle are needed to withdraw the medicinal product from the vial. OPDIVO solution for injection may be administered subcutaneously using a 23G-25G hypodermic injection needle or subcutaneous administration set (e.g., winged/butterfly).

If a dose of 600 mg is to be administered, allow 1 vial to reach room temperature, then withdraw 5 mL of OPDIVO solution for injection into the syringe.

If a dose of 1200 mg is to be administered, allow 2 vials to reach room temperature, then withdraw 10 mL of OPDIVO solution for injection into the syringe.

The hypodermic injection needle must be attached to the syringe immediately prior to administration to avoid clogging.

It is recommended to use the prepared dose immediately.

If storage is required (see section 6.3), apply a syringe tip cap prior to storage.

If stored in the refrigerator, allow the solution to reach ambient temperature before administration.

Disposal
Discard any unused solution remaining in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015
Date of latest renewal: 23 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

Name and address of the manufacturer responsible for batch release

Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the patient alert card.

- **The patient alert card** shall contain the following key messages:

- That OPDIVO treatment may increase the risk of:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related nephritis and renal dysfunction
  - Immune-related endocrinopathies
  - Immune-related skin adverse reactions
  - Other immune-related ARs

- Signs or symptoms of the safety concern and when to seek attention from a HCP

- Contact details of the OPDIVO prescriber

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
1. Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	By 28th February 2026
2. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer, the MAH should submit the OS data from the second interim analysis and the final OS analysis of the Phase III study CA209577.	By 30th June 2025
3. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as neoadjuvant treatment of adults with non-small cell lung cancer, the MAH should submit the OS data from the final OS analysis of the Phase 3 study CA209816.	By 30th June 2025
4. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma, the MAH should submit the OS data from the 2nd IA and the final OS analysis of the Phase 3 CA209274 study in the PD-L1 $\geq$ 1% population.	By 31st December 2027

5. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K.	By 31st March 2029
6. Post authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%, the MAH should submit the results of the final OS analysis from study CA20977T, a phase III, randomised, double-blind study.	By 30th June 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 10 mg of nivolumab.
Each vial of 4 mL contains 40 mg of nivolumab.
Each vial of 10 mL contains 100 mg of nivolumab.
Each vial of 12 mL contains 120 mg of nivolumab.
Each vial of 24 mL contains 240 mg of nivolumab.

3. LIST OF EXCIPIENTS

Excipients: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid, water for injections.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

40 mg/4 mL
100 mg/10 mL
120 mg/12 mL
240 mg/24 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001 40 mg vial
EU/1/15/1014/002 100 mg vial
EU/1/15/1014/003 240 mg vial
EU/1/15/1014/004 120 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 600 mg solution for injection
Nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 600 mg of nivolumab in 5 mL solution.
Each mL of solution for injection contains 120 mg of nivolumab.

3. LIST OF EXCIPIENTS

Excipients: recombinant human hyaluronidase (rHuPH20), histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, methionine, water for injection. See leaflet for further information before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

600 mg/5 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use only.
For single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL sterile concentrate
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 10 mg of nivolumab.
Each vial of 12 mL contains 120 mg of nivolumab.
Each vial of 24 mL contains 240 mg of nivolumab.

3. LIST OF EXCIPIENTS

Excipients: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

120 mg/12 mL
240 mg/24 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
IV use
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/003 240 mg vial
EU/1/15/1014/004 120 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

OPDIVO 10 mg/mL sterile concentrate
nivolumab
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
For single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/4 mL
100 mg/10 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

OPDIVO 600 mg solution for injection
Nivolumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

600 mg/5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the alert card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What OPDIVO is and what it is used for
2. What you need to know before you use OPDIVO
3. How to use OPDIVO
4. Possible side effects
5. How to store OPDIVO
6. Contents of the pack and other information

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat:
- advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older
- melanoma after complete resection in adults and adolescents 12 years of age and older (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- non-small cell lung cancer (a type of lung cancer) prior to resection in adults (treatment prior to surgery is called neoadjuvant therapy)
- non-small cell lung cancer (a type of lung cancer) prior to resection and after resection in adults (treatment prior to surgery is called neoadjuvant therapy; treatment after surgery is called adjuvant therapy)
- malignant pleural mesothelioma (a type of cancer that affects the lining of the lung) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- classical Hodgkin lymphoma that has come back after or has not responded to previous therapies, including an autologous stem-cell transplant (a transplant of your own blood-producing cells) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- urothelial carcinoma after complete resection in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- oesophageal (gullet) or gastro-oesophageal junction cancer with residual pathologic disease after chemoradiation followed by surgery in adults
- advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (stomach or gullet cancer) in adults
- unresectable or advanced hepatocellular carcinoma (liver cancer) in adults.

It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching

off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck, bladder, colon, rectal, stomach, oesophageal or gastro-oesophageal junction cancer cells.

OPDIVO may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, please ask your doctor.

2. What you need to know before you use OPDIVO

You should not be given OPDIVO
- if you are **allergic** to nivolumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.
- **Diabetes** including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Graft-versus-host disease.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your doctor may
- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of OPDIVO,
- or stop your treatment with OPDIVO altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during your treatment.

Check with your doctor or nurse before you are given OPDIVO if:
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have **melanoma of the eye**;
- you were previously given ipilimumab, another medicine for treating melanoma, and experienced **serious side effects** because of that medicine;
- you have been told that your **cancer has spread to your brain;**
- you have any history of **inflammation of the lungs**;
- you have been taken **medicines to suppress your immune system.**

OPDIVO acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO. These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

Children and adolescents
OPDIVO should not be used in children and adolescents below 18 years of age except for adolescents 12 years of age and older with melanoma.

Other medicines and OPDIVO
Before you are given OPDIVO, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of OPDIVO. However, once you are treated with OPDIVO, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.
Tell your doctor if you are taking or have recently taken any other medicines. **Do not take any other medicines** during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

Do not use OPDIVO if you are pregnant unless your doctor specifically tells you to. The effects of OPDIVO in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with OPDIVO and for at least 5 months following the last dose of OPDIVO, if you are a woman who could become pregnant.
- If you become pregnant while using OPDIVO **tell your doctor**.

It is not known whether OPDIVO gets into breast milk. A risk to the breast-fed infant cannot be excluded. **Ask your doctor** if you can breast-feed during or after treatment with OPDIVO.

Driving and using machines
OPDIVO or OPDIVO in combination with ipilimumab may have a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that OPDIVO does not adversely affect you.

OPDIVO contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given OPDIVO. This medicine contains 2.5 mg sodium (main component of cooking/table salt) in each mL of concentrate. OPDIVO contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the recommended maximum daily dietary intake of sodium for an adult.

You will also find key messages from this package leaflet in the patient alert card you have been given by your doctor. It is important that you keep this patient alert card and show it to your partner or caregivers.

3. How to use OPDIVO

How much OPDIVO is given
When OPDIVO is given on its own, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks depending on indication.

When OPDIVO is given on its own, for the treatment of skin cancer in adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks. For adolescents 12 years of age and older and weighing less than 50 kg, the recommended dose is either 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer in adults and adolescents 12 years of age and older, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO (single-agent phase) is 240 mg given every 2 weeks or 480 mg given every 4 weeks in adults and adolescents 12 years of age and older and weighing at least 50 kg or 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks for adolescents 12 years of age and older and weighing less than 50 kg.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced colon or rectal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight or 240 mg for the first 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg every 4 weeks (single-agent phase) depending on your treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight every 2 weeks or 360 mg every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of unresectable or advanced liver cancer, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for up to 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg every 4 weeks (single agent phase) depending on your treatment.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant treatment of non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant and adjuvant treatment of non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks prior to resection and 480 mg every 4 weeks after surgery.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 240 mg every 2 weeks or 480 mg every 4 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the recommended dose of OPDIVO is 360 mg every 3 weeks or 240 mg every 2 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, the recommended dose of OPDIVO is 360 mg nivolumab every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks.

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of advanced non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks. After completion of 2 cycles of chemotherapy, OPDIVO is given in combination with ipilimumab, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks.

Depending on your dose, the appropriate amount of OPDIVO will be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. More than one vial of OPDIVO may be necessary to obtain the required dose.

How OPDIVO is given
You will receive treatment with OPDIVO in a hospital or clinic, under the supervision of an experienced doctor.

OPDIVO will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving. Your doctor will continue giving you OPDIVO for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of skin, advanced kidney advanced colon or rectal cancer, or unresectable or advanced liver cancer you will be given an infusion over a period of 30 minutes, every 3 weeks for up to 4 doses (combination phase) depending on your treatment. Thereafter it will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes, every 2 or 3 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant treatment of non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given after surgery as adjuvant treatment of non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 4 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes, every 2 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, you will be given an infusion over a period of 30 minutes every 3 weeks or every 2 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, you will be given an infusion over a period of 30 minutes every 2, 3 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of advanced non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given in combination with cabozantinib, you will be given an infusion over a period of 30 minutes or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

If you miss a dose of OPDIVO
It is very important for you to keep all your appointments to receive OPDIVO. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using OPDIVO
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with OPDIVO unless you have discussed this with your doctor.

If you have any further questions about your treatment or on the use of this medicine, ask your doctor.

When OPDIVO is given in combination with other anti-cancer medicines, you will first be given OPDIVO followed by the other medicine.

Please refer to the package leaflet of these other medicines in order to understand the use of these medicines. If you have questions about them, please ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation. OPDIVO acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of OPDIVO.

The following side effects have been reported **with OPDIVO alone:**

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Decreased appetite, high sugar levels in the blood (hyperglycaemia)
- Headache
- Shortness of breath (dyspnoea), cough

- Diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain, constipation
- Skin rash sometimes with blisters, itching
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Feeling tired or weak, fever

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis
- Reactions related to the infusion of the medicine, allergic reaction (including life-threatening allergic reaction)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), swelling of the thyroid gland
- Dehydration, decrease in body weight, low sugar levels in the blood (hypoglycaemia)
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Blurred vision, dry eyes
- Fast heart rate, abnormal heart rhythm
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, oedema (swelling)

Uncommon (may affect up to 1 in 100 people)
- Increase in some white blood cells
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, diabetes
- Increased acid levels in the blood (metabolic acidosis)
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness)
- Inflammation of the heart muscle, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders), changes in the rhythm or rate of the heartbeat
- Fluid in the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis), blockage of bile ducts (cholestasis)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

Rare (may affect up to 1 in 1000 people)
- A temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Acid in the blood produced from diabetes (diabetic ketoacidosis), decreased function of the parathyroid gland

- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome), inflammation of the brain
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammatory disease of blood vessels
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)

The following side effects have been reported **with OPDIVO in combination with other anti-cancer medicines** (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite, decrease in body weight, decreased levels of albumin in the blood, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness, altered sense of taste
- High blood pressure (hypertension)
- Shortness of breath (dyspnoea), cough, abnormal speaking sound (dysphonia)
- Diarrhoea (watery, loose or soft stools), constipation, vomiting, nausea, stomach pain, mouth ulcers and cold sores (stomatitis), indigestion (dyspepsia)

- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet: rash or redness of the skin, tingling and tenderness developing to symmetrical redness, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysaesthaesia syndrome)
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain), muscle spasm
- Excess protein in urine
- Feeling tired or weak, fever, oedema (swelling)

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, decreased levels of phosphate in the blood
- Sensations like numbness and tingling (paraesthesia)
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Blurred vision, dry eye
- Fast heart rate, abnormal heart rhythm, inflammatory disease of blood vessels
- Formation of a blood clot within a blood vessel (thrombosis)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, nose bleeding
- Inflammation of the intestines (colitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis), oral pain, haemorrhoids (piles)
- Inflammation of the liver
- Skin colour change in patches (including vitiligo), redness of the skin, unusual hair loss or thinning, hair colour change, hives (itchy rash), discolouration or abnormal darkening of the skin (skin hyperpigmentation), dry skin
- Inflammation of the joints (arthritis), muscle weakness, aching muscles
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, chills
- Feeling generally unwell (malaise)

Uncommon (may affect up to 1 in 100 people)
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis or syndrome)
- Inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Changes in the rhythm or rate of the heartbeat, slow heart rate, inflammation of the heart muscle
- Intestinal perforation, inflammation of the duodenum, burning or painful sensation in the tongue (glossodynia)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (other lichen disorders)
- Muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, inflammation of the muscles causing pain or

stiffness (polymyalgia rheumatica), bone damage in the jaw, abnormal opening between two body parts, such as an organ or blood vessel and another structure (fistula)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Rare (may affect up to 1 in 1000 people)
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammation of the nerves
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus)
- Chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), muscle spasm (rhabdomyolysis)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Changes in test results
OPDIVO alone or in combination may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium

- Increased amount of thyroid stimulating hormone
- Increase in blood triglyceride levels in the blood
- Increase in cholesterol levels in the blood

Reporting of side effects
If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store OPDIVO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What OPDIVO contains
- The active substance is nivolumab.

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
Each vial contains either 40 mg (in 4 mL), 100 mg (in 10 mL), 120 mg (in 12 mL) or 240 mg (in 24 mL) of nivolumab.

- The other ingredients are sodium citrate dihydrate, sodium chloride (see section 2 "OPDIVO contains sodium"), mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid and water for injections.

What OPDIVO looks like and contents of the pack
OPDIVO concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing either 1 vial of 4 mL, 1 vial of 10 mL, 1 vial of 12 mL or 1 vial of 24 mL.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu

The following information is intended for healthcare professionals only:

Preparation and administration of OPDIVO

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose
More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

Nivolumab monotherapy

The prescribed dose for adults is 240 mg or 480 mg given regardless of body weight depending on indication.

Melanoma (advanced or adjuvant treatment) in adolescents. The prescribed dose for adolescents 12 years of age and older weighing at least 50 kg is 240 mg or 480 mg. For adolescents 12 years of age and older and weighing less than 50 kg the prescribed dose is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The **total nivolumab dose** in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The **volume of OPDIVO concentrate** to prepare the dose (mL) = the total nivolumab dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

Nivolumab in combination with ipilimumab

The **prescribed dose** for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given (please see above).

Nivolumab in combination with ipilimumab in malignant pleural mesothelioma

The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in advanced colorectal cancer

The prescribed dose for the patient can be based on body weight (3 mg/kg) or can be 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in advanced oesophageal cancer

The prescribed dose for the patient can be based on body weight (3 mg/kg) or is 360 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in unresectable or advanced liver cancer

The prescribed dose for the patient is based on body weight (1 mg/kg).

Nivolumab in combination with chemotherapy in resectable non-small cell lung cancer

The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in advanced oesophageal cancer

The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab and chemotherapy

The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with cabozantinib

The prescribed dose for the patient is nivolumab 240 mg or 480 mg given regardless of body weight.

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion.

OPDIVO can be used for intravenous administration either:
- **without dilution,** after transfer to an infusion container using an appropriate sterile syringe;

or
- **after diluting** according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

- OPDIVO concentrate may be diluted with either:
  - sodium chloride 9 mg/mL (0.9%) solution for injection; or
  - 50 mg/mL (5%) glucose solution for injection.

STEP 1
- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.

Administer the OPDIVO infusion **intravenously over a period of 30 or 60 minutes depending on the dose and the indication**.

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm).

OPDIVO infusion is compatible with:
- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Storage conditions and shelf life

Unopened vial

OPDIVO must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. OPDIVO should not be frozen.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Do not use OPDIVO after the expiry date which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.

OPDIVO infusion

Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	**Chemical and physical in-use stability**	
	Storage at 2ºC to 8ºC protected from light	**Storage at room temperature (≤ 25°C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	8 hours (of total 7 days storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature (≤ 25°C). Aseptic handling should be ensured during the preparation of infusion.

Disposal
Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

OPDIVO 600 mg solution for injection
nivolumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the alert card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What OPDIVO is and what it is used for
2. What you need to know before you use OPDIVO
3. How to use OPDIVO
4. Possible side effects
5. How to store OPDIVO
6. Contents of the pack and other information

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat:
- advanced melanoma (a type of skin cancer) in adults
- melanoma after complete resection in adults (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- urothelial carcinoma after complete resection in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- oesophageal (gullet) or gastro-oesophageal junction cancer with residual pathologic disease after chemoradiation followed by surgery in adults
- advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (stomach or gullet cancer) in adults.

It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body’s natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma, lung, kidney, head and neck, bladder, colon, rectal, stomach, oesophageal or gastro-oesophageal junction cancer cells.

OPDIVO may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, please ask your doctor.

2. What you need to know before you use OPDIVO

You should not be given OPDIVO
- if you are **allergic** to nivolumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.
- **Diabetes** including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Graft-versus-host disease.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your doctor may
- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of OPDIVO,
- or stop your treatment with OPDIVO altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during your treatment.

Check with your doctor or nurse before you are given OPDIVO if:
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have **melanoma of the eye**;

- you were previously given ipilimumab, another medicine for treating melanoma, and experienced **serious side effects** because of that medicine;
- you have been told that your **cancer has spread to your brain;**
- you have any history of **inflammation of the lungs**;
- you have been taking **medicines to suppress your immune system.**

OPDIVO acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO. These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

Children and adolescents
OPDIVO solution for injection should not be used in children and adolescents below 18 years of age.

Other medicines and OPDIVO
Before you are given OPDIVO, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of OPDIVO. However, once you are treated with OPDIVO, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.
Tell your doctor if you are taking or have recently taken any other medicines. **Do not take any other medicines** during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

Do not use OPDIVO if you are pregnant unless your doctor specifically tells you to. The effects of OPDIVO in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with OPDIVO and for at least 5 months following the last dose of OPDIVO, if you are a woman who could become pregnant.
- If you become pregnant while using OPDIVO **tell your doctor**.

It is not known whether OPDIVO gets into breast milk. A risk to the breast-fed infant cannot be excluded. **Ask your doctor** if you can breast-feed during or after treatment with OPDIVO.

Driving and using machines
OPDIVO or OPDIVO in combination with ipilimumab may have a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that OPDIVO does not adversely affect you.

OPDIVO contains polysorbate 80 (E433)
This medicine contains 2.5 mg of polysorbate 80 in each 5 mL vial which is equivalent to 5 mg/10 mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

You will also find key messages from this package leaflet in the patient alert card you have been given by your doctor. It is important that you keep this patient alert card and show it to your partner or caregivers.

3. How to use OPDIVO

How much OPDIVO is given
When OPDIVO is given on its own as an injection under your skin (subcutaneous injection), the recommended dose is either 600 mg given every 2 weeks or 1200 mg given every 4 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer, the recommended dose of OPDIVO given as an infusion into a vein is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO given as an infusion into a vein is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced colon or rectal cancer, the recommended dose of OPDIVO given as an infusion into a vein is 3 mg of nivolumab per kilogram of your body weight or 240 mg for the first 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase) depending on your treatment.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 600 mg every 2 weeks or 1200 mg every 4 weeks as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the recommended dose of OPDIVO is 600 mg every 2 weeks as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, the recommended dose of OPDIVO given as an infusion into a vein is 360 mg nivolumab every 3 weeks for up to 6 cycles (combination phase). Thereafter, the recommended dose of OPDIVO given as an injection under your skin is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 600 mg given every 2 weeks or 1200 mg given every 4 weeks as an injection under your skin.

How OPDIVO is given
You will receive treatment with OPDIVO under the supervision of an experienced doctor. More than one vial of OPDIVO may be necessary to obtain the required dose.

OPDIVO is given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving. Treatment with OPDIVO will continue for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of skin, advanced kidney or advanced colon or rectal cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks for the first 4 doses (combination phase). Thereafter, it will be given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of advanced oesophageal cancer, it will be given over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, it will be given over a period of 3 to 5 minutes every 2 weeks.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of urothelial carcinoma, it will be given over a period of 3 to 5 minutes every 2 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with cabozantinib, it will be given over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

If you miss a dose of OPDIVO
It is very important for you to keep all your appointments to receive OPDIVO. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using OPDIVO
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with OPDIVO unless you have discussed this with your doctor.

If you have any further questions about your treatment or on the use of this medicine, ask your doctor.

When OPDIVO is given in combination with other anti-cancer medicines, you will first be given OPDIVO followed by the other medicine.

Please refer to the package leaflet of these other medicines in order to understand the use of these medicines. If you have questions about them, please ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation. OPDIVO acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of OPDIVO.

The following side effects have been reported **with OPDIVO alone:**

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Decreased appetite, high sugar levels in the blood (hyperglycaemia)
- Headache
- Shortness of breath (dyspnoea), cough
- Diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain, constipation
- Skin rash sometimes with blisters, itching
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Feeling tired or weak, fever

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis
- Reactions related to the infusion of the medicine, allergic reaction, (including life-threatening allergic reaction)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), swelling of the thyroid gland
- Dehydration, decrease in body weight, low sugar levels in the blood (hypoglycaemia)
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Blurred vision, dry eyes
- Fast heart rate, abnormal heart rhythm
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, oedema (swelling)
- Reaction at site of injection

Uncommon (may affect up to 1 in 100 people)
- Increase in some white blood cells
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, diabetes
- Increased acid levels in the blood (metabolic acidosis)
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness)
- Inflammation of the heart muscle, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders), changes in the rhythm or rate of the heartbeat
- Fluid in the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis), blockage of bile ducts (cholestasis)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

Rare (may affect up to 1 in 1 000 people)
- A temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Acid in the blood produced from diabetes (diabetic ketoacidosis), decreased function of the parathyroid gland
- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome), inflammation of the brain

- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammatory disease of blood vessels
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)

The following side effects have been reported **with OPDIVO in combination with other anti-cancer medicines** (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite, decrease in body weight, decreased levels of albumin in the blood, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness, altered sense of taste
- High blood pressure (hypertension)
- Shortness of breath (dyspnoea), cough, abnormal speaking sound (dysphonia)
- Diarrhoea (watery, loose or soft stools), constipation, vomiting, nausea, stomach pain, mouth ulcers and cold sores (stomatitis), indigestion (dyspepsia)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet: rash or redness of the skin, tingling and tenderness developing to symmetrical redness, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysaesthaesia syndrome)

- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain), muscle spasm
- Excess protein in urine
- Feeling tired or weak, fever, oedema (swelling)

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, decreased levels of phosphate in the blood
- Sensations like numbness and tingling (paraesthesia)
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Blurred vision, dry eye
- Fast heart rate, abnormal heart rhythm, inflammatory disease of blood vessels
- Formation of a blood clot within a blood vessel (thrombosis)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, nose bleeding
- Inflammation of the intestines (colitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis), oral pain, haemorrhoids (piles)
- Inflammation of the liver
- Skin colour change in patches (including vitiligo), redness of the skin, unusual hair loss or thinning, hair colour change, hives (itchy rash), discolouration or abnormal darkening of the skin (skin hyperpigmentation), dry skin
- Inflammation of the joints (arthritis), muscle weakness, aching muscles
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, chills
- Feeling generally unwell (malaise)

Uncommon (may affect up to 1 in 100 people)
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis or syndrome), inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Changes in the rhythm or rate of the heartbeat, slow heart rate, inflammation of the heart muscle
- Intestinal perforation, inflammation of the duodenum, burning or painful sensation in the tongue (glossodynia)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (other lichen disorders)
- Muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), bone damage in the jaw, abnormal opening between two body parts, such as an organ or blood vessel and another structure (fistula)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Rare (may affect up to 1 in 1 000 people)
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammation of the nerves
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus)
- Chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), muscle spasm (rhabdomyolysis)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Changes in test results
OPDIVO alone or in combination may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Increased amount of thyroid stimulating hormone
- Increase in blood triglyceride levels in the blood
- Increase in cholesterol levels in the blood

Reporting of side effects
If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store OPDIVO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

Do not store any unused portion of the injection solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What OPDIVO contains
- The active substance is nivolumab.

Each mL of solution for injection contains 120 mg of nivolumab.
Each vial contains 600 mg (in 5 mL) of nivolumab.

The other ingredients are recombinant human hyaluronidase (rHuPH20), histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80 (E433), methionine, and water for injection (see section 2 “OPDIVO contains polysorbate 80 (E433)”).

What OPDIVO looks like and contents of the pack
OPDIVO solution for injection is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing 1 glass vial of 5 mL.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

To prevent medication errors, it is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient as prescribed.

Preparation and administration of OPDIVO

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose
More than one vial of OPDIVO may be needed to give the total dose for the patient.

Nivolumab monotherapy
The prescribed dose for the patient is 600 mg or 1200 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in advanced oesophageal cancer
The prescribed dose for the patient is 600 mg or 1200 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The prescribed dose for the patient is 600 mg given regardless of body weight.

Nivolumab in combination with cabozantinib
The prescribed dose for the patient is nivolumab 600 mg or 1200 mg given regardless of body weight.

Preparing the injection
- Inspect the vial of OPDIVO solution for injection for particulate matter or discolouration. Do not shake the vial. OPDIVO solution for injection is a clear to opalescent, colourless to yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Allow the vial or vials (depending on the prescribed dose) to reach room temperature.
- Withdraw the required volume of OPDIVO solution for injection using an appropriate sterile syringe and transfer needle.

Administration
OPDIVO solution for injection must not be administered intravenously.

Administer the OPDIVO solution for injection subcutaneously via a 23G-25G hypodermic needle or subcutaneous administration set (e.g., winged/butterfly) **over a period of 3 to 5 minutes** into the subcutaneous tissue of the abdomen or thigh.

Alternate injection sites for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration is interrupted, continue administering at the same site, or at an alternate site.

Do not administer other subcutaneous medicines at the same site used for OPDIVO solution for injection.

OPDIVO solution for injection is compatible with:
- Polypropylene
- Polycarbonate
- Polyethylene
- Polyurethane
- Polyvinyl chloride
- Fluorinated ethylene propylene
- Stainless steel

Storage conditions and shelf life

Unopened vial

OPDIVO must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. OPDIVO should not be frozen.

Do not use OPDIVO after the expiry date which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.

Storage in the syringe

From a microbiological point of view, once transferred from the vial to the syringe, the medicinal product should be used immediately since the medicine does not contain any antimicrobial-preservative or bacteriostatic agents. If not used immediately, OPDIVO solution for injection transferred to the syringe can be stored in the refrigerator at 2°C to 8°C, protected from light for up to 7 days and/or at room temperature 20°C to 25°C and room light for up to 8 hours. Discard if storage time exceeds these limits. Aseptic handling should be ensured during the preparation of the syringe for injection.

Disposal

Do not store any unused portion of the injection solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

BRISTOL-MYERS SQUIBB COMPANY

COMPANY CORE DATA SHEET

(CCDS)

NIVOLUMAB

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