ヤーボイ点滴静注液20mg、同点滴静注液50mg
に関する資料

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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

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 外国における使用状況等に関する資料

1.1 外国における使用状況

イピリムマブ（遺伝子組換え）（以下、イピリムマブ）は、2011 年 3 月 25 日に米国で最初に承認され、その後 EU では 2011 年 7 月 13 日に承認されている（Table 1.1-1）。2025 年 5 月時点で、世界 60 以上の国と地域で承認されている。

一次治療の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治癒不能な進行・再発の結腸・直腸がんに対してニボルマブ（遺伝子組み換え）とイピリムマブの併用療法が中国で 2024 年 10 月に承認されて以降、米国及び EU を含む 6 つの国又は地域で承認されている。米国及び EU におけるイピリムマブの効能又は効果並びに用法及び用量を Table 1.1-2 に示した。

Table 1.1-1: 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／含量	最初の承認年月日
米国	YERVOY (ipilimumab) injection, for intravenous use	50 mg/10 mL (5 mg/mL) 200 mg/40 mL (5 mg/mL)	2011 年 3 月 25 日
EU	YERVOY 5 mg/ml concentrate for solution for infusion	50 mg/10 ml 200 mg/40 ml	2011 年 7 月 13 日

Table 1.1-2: 主要な既承認国（米国及び EU）における効能又は効果並びに用法及び用量

国名	承認年月日	効能又は効果	用法及び用量
米国	2025 年 4 月 8 日	YERVOY, in combination with nivolumab, 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) ~~metastatic~~ colorectal cancer (~~m~~CRC) ~~that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan~~.	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 1 mg/kg every 3 weeks‡ with nivolumab 240 mg‡ Pediatric patients age 12 years and older and weighing less than 40 kg: 1 mg/kg every 3 weeks‡ with nivolumab 3 mg/kg‡ In combination with nivolumab for a maximum of 4 doses.† After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression ~~or,~~ unacceptable toxicity, or up to 2 years.† †Refer to the Prescribing Information for nivolumab for dosage information after completing use in combination with YERVOY. ‡30-minute intravenous infusion on the same day.
EU[a)]	2024 年 12 月 19 日	YERVOY in combination with nivolumab is indicated for the treatment of	The recommended dose for first-line treatment of dMMR or MSI-H CRC is 1 mg/kg ipilimumab in combination with 240 mg of nivolumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy is

		adult patients with mismatch repair deficient or microsatellite instability-high ~~metastatic~~ 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	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 ipilimumab and nivolumab.

a）中央承認審査方式により審査 （取消線：既承認の事項からの削除、下線：既承認の事項からの追加）

1.2 外国の添付文書及び企業中核データシート（CCDS）

［CCDS］、米国添付文書（USPI）の［原文］と［邦訳（概略）］及び欧州製品概要（SmPC）の［原文］と［邦訳（概略）］を添付する。

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

YERVOY® (ipilimumab) injection, for intravenous use
Initial U.S. Approval: 2011

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

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

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

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:

Melanoma

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab. (1.1)
- Adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. (1.2)

Renal Cell Carcinoma (RCC)

- Treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab. (1.3)

Colorectal Cancer

- Treatment of adults and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) in combination with nivolumab. (1.4)

Hepatocellular Carcinoma

- adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) as first-line treatment in combination with nivolumab. (1.5)
- in combination with nivolumab in adult patients with unresectable or metastatic HCC who have been previously treated with sorafenib. (1.5)

Non-Small Cell Lung Cancer (NSCLC)

- Treatment of 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 nivolumab. (1.6)
- Treatment of 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 nivolumab and 2 cycles of platinum-doublet chemotherapy. (1.6)

Malignant Pleural Mesothelioma

- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab. (1.7)

Esophageal Cancer

- Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first line treatment in combination with nivolumab whose tumors express PD-L1 (≥1). (1.8)

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

- Administer by intravenous infusion after dilution based upon recommended infusion rate for each indication. (2)
- Unresectable or Metastatic Melanoma:
  - YERVOY 3 mg/kg every 3 weeks for a maximum of 4 doses. (2.2)
  - YERVOY 3 mg/kg immediately following nivolumab 1 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in the Full Prescribing Information for nivolumab. (2.2)
- Adjuvant Treatment of Melanoma: YERVOY 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 12 weeks for up to 4 additional doses. (2.2)
- Advanced Renal Cell Carcinoma: YERVOY 1 mg/kg immediately following nivolumab 3 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
- Treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in combination with nivolumab:
  - Adult and pediatric patients weighing 40 kg or greater: YERVOY 1 mg/kg immediately following nivolumab 240 mg on the same day every 3 weeks for a maximum of 4 doses. After completing the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
  - Pediatric patients weighing less than 40 kg: YERVOY 1 mg/kg immediately following nivolumab 3 mg/kg on the same day every 3 weeks for a maximum of 4 doses. After completing the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
- Hepatocellular Carcinoma: YERVOY 3 mg/kg intravenously over 30 minutes immediately following nivolumab 1 mg/kg intravenously over 30 minutes on the same day, every 3 weeks for up to 4 doses. After completing up to 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
- Metastatic non-small cell lung cancer:
  - YERVOY 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks. (2.2)
  - YERVOY 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks and 2 cycles of platinum-doublet chemotherapy. (2.2)
- Malignant pleural mesothelioma: YERVOY 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks. (2.2)
- Esophageal squamous cell carcinoma: YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks. (2.2)
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

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

- Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) in a single-dose vial. (3)

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

- None. (4)

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

- Severe and Fatal Immune-Mediated Adverse Reactions: Immune-mediated adverse reactions (IMAR) can occur in any organ system or tissue, including the following: immune-mediated colitis, immune-mediated hepatitis, immune-mediated dermatologic adverse reactions, immune-mediated endocrinopathies, immune-mediated pneumonitis, and immune-mediated nephritis with renal dysfunction, and can occur at any time during treatment or after discontinuation. Monitor for symptoms and signs that may be clinical manifestations of IMAR. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function including at baseline and before each dose. In general, withhold YERVOY for severe (grade 3) and permanently discontinue for life-threatening (grade 4) immune-mediated adverse reactions. See Full Prescribing Information for additional dosage modifications. (2.3, 5.1)
- Infusion-Related Reactions: Discontinue for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. (2.3, 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 YERVOY. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

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

Most common adverse reactions (≥20%) with YERVOY as a single agent are fatigue, diarrhea, pruritus, rash, nausea, and headache. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab are 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)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab and platinum-doublet chemotherapy are fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (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.

Revised: 5/2025

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- 1.2 Adjuvant Treatment of Melanoma
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

1.2 Adjuvant Treatment of Melanoma

YERVOY is indicated for the adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

1.3 Advanced Renal Cell Carcinoma

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

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

- YERVOY, in combination with nivolumab, 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).

1.5 Hepatocellular Carcinoma

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

1.6 Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (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.

YERVOY, in combination with nivolumab 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.

1.7 Malignant Pleural Mesothelioma

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

1.8 Esophageal Cancer

YERVOY, in combination with nivolumab, 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)]*.

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 YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.6)]*.

Esophageal Cancer

- Select patients with unresectable or advanced or metastatic ESCC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.8)]*.
- An FDA-approved companion diagnostic for the detection of PD-L1 expression in patients with advanced or metastatic ESCC is not available.

2.2 Recommended Dosage

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

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

Table 1: Recommended Dosages for YERVOY as a Single Agent

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks	Maximum of 4 doses
Adjuvant treatment of melanoma	3 mg/kg every 3 weeks followed by 3 mg/kg every 12 weeks	Every 3 weeks up to a maximum of 4 doses Every 12 weeks for up to 4 additional doses

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

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

Table 2: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents*

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks with nivolumab 1 mg/kg	In combination with nivolumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier. After completing 4 doses of combination therapy, administer nivolumab as a single agent until disease progression or unacceptable toxicity.†
Advanced renal cell carcinoma	1 mg/kg every 3 weeks with nivolumab 3 mg/kg	In combination with nivolumab for a maximum of 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity.†
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: 1 mg/kg every 3 weeks with nivolumab 240 mg	In combination with nivolumab for a maximum of 4 doses.† After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression, unacceptable toxicity, or up to 2 years.†
	Pediatric patients age 12 years and older and weighing less than 40 kg: 1 mg/kg every 3 weeks with nivolumab 3 mg/kg	
Hepatocellular carcinoma	3 mg/kg every 3 weeks with nivolumab 1 mg/kg	In combination with nivolumab for a maximum of 4 doses. After completing a maximum of 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity.†
Metastatic non-small cell lung cancer expressing PD-L1	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.†
Metastatic or recurrent non-small cell lung cancer	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks and histology-based platinum-doublet chemotherapy every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.†
		2 cycles of histology-based platinum-doublet chemotherapy
Malignant pleural mesothelioma	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients

Table 2: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents*

Indication	Recommended YERVOY Dosage	Duration of Therapy
		without disease progression.†
Esophageal squamous cell carcinoma	1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years.

* Refer to the Prescribing Information for the agents administered in combination with YERVOY for recommended dosing information, as appropriate.

† Refer to the Prescribing Information for nivolumab for dosage information after completing use in combination with YERVOY.

2.3 Recommended Dosage Modifications for Adverse Reactions

No dose reduction for YERVOY is recommended. In general, withhold YERVOY for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue YERVOY for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (Grade 2) or severe (Grade 3) reactions lasting 12 weeks or longer after last YERVOY dose (excluding endocrinopathy), 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 YERVOY or YERVOY in combination with nivolumab for adverse reactions that require management different from these general guidelines are summarized in Table 3.

When YERVOY is administered in combination with nivolumab, withhold or permanently discontinue both YERVOY and nivolumab for toxicity.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
Immune-Mediated Adverse Reactions *[See Warnings and Precautions (5.1)]*		
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 or ALT increases to more than 3 times and up to 5 times the ULN or Total bilirubin increases to more than 1.5 times and up to 3 times the ULN	Withhold[a]
	AST or ALT more than 5 times the ULN or Total bilirubin more than 3 times the ULN	Permanently discontinue

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
Hepatitis with tumor involvement of the liver[b]/HCC[c]	Baseline AST/ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST/ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN.	Withhold[a]
	AST/ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Endocrinopathies[d]	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires systemic treatment	Permanently discontinue
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

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 of normal

* Based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

[a] Resume in patients with complete or partial resolution (Grade 0 or 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/ALT are less than or equal to ULN at baseline, withhold or permanently discontinue YERVOY based on recommendations for hepatitis with no liver involvement.

[c] This guidance is only applicable to HCC patients who are being treated with YERVOY in combination with nivolumab.

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

2.4 Preparation and Administration

- Do not shake product.
- Visually inspect for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vial(s) to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a **final concentration ranging from 1 mg/mL to 2 mg/mL**. Mix diluted solution by gentle inversion.
- After preparation, store the diluted solution either refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature of 20°C to 25°C (68°F to 77°F) for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used or empty vials of YERVOY.

Administration

- Do not co-administer other drugs through the same intravenous line.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted YERVOY solution by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.
- When administered in combination with nivolumab, infuse nivolumab first followed by YERVOY on the same day.
- When administered with nivolumab and platinum-doublet chemotherapy, infuse nivolumab first followed by YERVOY and then platinum-doublet chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) as a clear to slightly 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

YERVOY is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for

induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of 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 YERVOY. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of YERVOY.

Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.3)]*. In general, if YERVOY 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.

Immune-Mediated Colitis

YERVOY can cause immune-mediated colitis, which may be fatal. 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.

YERVOY 3 mg/kg as a Single Agent

Immune-mediated colitis occurred in 12% (62/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (7%) and Grade 2 (5%). Colitis led to permanent discontinuation of YERVOY in 4.3% and withholding of at least one dose of YERVOY in 0.2% of patients.

Systemic corticosteroids were required in 74% (46/62) of patients with immune-mediated colitis. Five patients required coadministration of another immunosuppressant with corticosteroids. Colitis resolved in 76% of the 62 patients. One patient was withheld one or more doses of YERVOY for colitis, and no patient received additional treatment after symptom improvement.

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated colitis occurred in 9% (60/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (4.4%), and Grade 2 (3.7%). Colitis led to permanent discontinuation of YERVOY and nivolumab in 3.2% and withholding of YERVOY and nivolumab in 2.7% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated colitis. Systemic

corticosteroids were therefore required in 100% (60/60) of patients with immune-mediated colitis. Approximately 23% of patients required coadministration of another immunosuppressant with corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom YERVOY or nivolumab was withheld for colitis, 16 received additional treatment after symptom improvement; of these, 10 had recurrence of colitis.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated colitis occurred in 25% (115/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 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 YERVOY with nivolumab in 14% and withholding of treatment 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 115 patients. Of the 20 patients in whom YERVOY with nivolumab was withheld for colitis, 16 reinitiated treatment after symptom improvement, and 9 had recurrence of colitis.

Immune-Mediated Hepatitis

YERVOY 3 mg/kg as a Single Agent

Immune-mediated hepatitis occurred in 4.1% (21/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (1.6%) and Grade 2 (2.5%). Hepatitis led to permanent discontinuation of YERVOY in 0.4% of patients and withholding of at least one dose of YERVOY in none of the patients.

Systemic corticosteroids were required in 29% (6/21) of patients with immune-mediated hepatitis. No patients required the coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 86% of the 21 patients.

YERVOY 3 mg/kg with Vemurafenib

The safety and effectiveness of YERVOY in combination with vemurafenib have not been established *[see Indications and Usage (1)]*. In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg or 720 mg twice daily).

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated hepatitis occurred in 7% (48/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%). Hepatitis led to permanent discontinuation of YERVOY and nivolumab in 3.6% and withholding of YERVOY and nivolumab in 2.6% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated hepatitis. Systemic corticosteroids were therefore required in 100% (48/48) of patients with immune-mediated hepatitis. Approximately 19% of patients required coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17

patients in whom YERVOY or nivolumab was withheld for hepatitis, 14 received additional treatment after symptom improvement; of these, 10 had recurrence of hepatitis.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated hepatitis occurred in 15% (70/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 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 YERVOY with nivolumab in 8% and withholding of treatment 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 addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 70 patients. Of the 16 patients in whom YERVOY with nivolumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement, and 8 had recurrence of hepatitis.

Immune-Mediated Dermatologic Adverse Reactions

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.3)]*.

YERVOY 3 mg/kg as a Single Agent

Immune-mediated rash occurred in 15% (76/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (2.5%) and Grade 2 (12%). Rash led to permanent discontinuation of YERVOY in 0.2% and withholding of at least one dose of YERVOY in 1.4% of patients.

Systemic corticosteroids were required in 43% (33/76) of patients with immune-mediated rash. Rash resolved in 71% of the 76 patients. Of the 7 patients in whom YERVOY was withheld for rash, 3 received additional treatment after symptom improvement; of these, 1 had recurrence of rash.

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated rash occurred in 16% (108/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (3.5%) and Grade 2 (4.2%). Rash led to permanent discontinuation of YERVOY and nivolumab in 0.5% of patients and withholding of YERVOY and nivolumab in 2.0% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated rash. Systemic corticosteroids were therefore required in 100% (108/108) of patients. Rash resolved in 75% of 108 patients. Of the 13 patients in whom YERVOY or nivolumab was withheld for rash, 11 received additional treatment after symptom improvement; of these, 5 had recurrence of rash.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated rash occurred in 28% (127/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (4.8%) and Grade 2 (10%) adverse reactions. Immune-mediated rash led to permanent discontinuation of YERVOY with nivolumab in 0.4% and withholding of treatment 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 of patients. Of the 18 patients in whom YERVOY with nivolumab was withheld for rash, 15 reinitiated treatment after symptom improvement, and 8 had recurrence of rash.

Immune-Mediated Endocrinopathies

YERVOY 3 mg/kg as a Single Agent

Grade 2-5 immune-mediated endocrinopathies occurred in 4% (21/511) of patients who received YERVOY 3 mg/kg as a single agent.

Severe to life-threatening (Grade 3-4) endocrinopathies occurred in 9 patients (1.8%). All 9 of these patients had hypopituitarism with some patients having additional concomitant endocrinopathies, such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies.

Moderate (Grade 2) endocrinopathy occurred in 12 patients (2.3%), including hypothyroidism, adrenal insufficiency, hypopituitarism, hyperthyroidism and Cushing's syndrome.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 required long-term hormone replacement therapy, including adrenal hormones (n=10) and thyroid hormones (n=13).

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Hypophysitis:

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

Hypophysitis occurred in 4.4% (29/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%). Hypophysitis led to permanent discontinuation of YERVOY and nivolumab in 1.2% and withholding of YERVOY with nivolumab in 2.1% of patients. Approximately 72% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 72% (21/29) of patients with immune-mediated hypophysitis. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom YERVOY or nivolumab was withheld for hypophysitis, 11 received additional treatment after symptom improvement; of these, 2 had recurrence of hypophysitis.

Adrenal Insufficiency:

Adrenal insufficiency occurred in 7% (48/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). Adrenal insufficiency led to permanent discontinuation of YERVOY with nivolumab in 1.2% and withholding of YERVOY with nivolumab in 2.1% of patients. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 94% (45/48) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom YERVOY or nivolumab was withheld for adrenal insufficiency, 11 received additional treatment after symptom improvement; of these, 2 had recurrence of adrenal insufficiency.

Hyperthyroidism:

Hyperthyroidism occurred in 12% (80/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (0.6%) and Grade 2 (4.5%). No patients discontinued YERVOY for hyperthyroidism. Hyperthyroidism led to withholding of YERVOY with nivolumab in 2.3% of patients. Approximately 19% received a thyroid synthesis inhibitor. 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 YERVOY or nivolumab was withheld for hyperthyroidism, 11 received additional treatment after symptom improvement; of these, 3 had recurrence of hyperthyroidism.

Hypothyroidism:

Hypothyroidism occurred in 18% (122/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (0.6%) and Grade 2 (11%). Hypothyroidism led to permanent discontinuation of YERVOY with nivolumab in 0.2% and withholding of YERVOY with nivolumab in 1.4% of patients. Approximately 82% received thyroid hormone replacement. 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 YERVOY or nivolumab was withheld for hypothyroidism, 5 received additional treatment after symptom improvement; of these, one patient had recurrence of hypothyroidism.

Thyroiditis:

Thyroiditis occurred in 2.7% (22/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (4.5%) and Grade 2 (2.2%). Thyroiditis led to permanent discontinuation of YERVOY with nivolumab in 0.2% and withholding of YERVOY with nivolumab in 0.8% of patients. Systemic corticosteroids were required in 18% (4/22) of patients with thyroiditis. Thyroiditis resolved in 64% of the 22 patients. Of the 5 patients in whom YERVOY or nivolumab was withheld for thyroiditis, 5 received additional treatment after symptom improvement; of these, no patients had recurrence of thyroiditis.

Type 1 Diabetes Mellitus:

Diabetes occurred in 2.7% (15/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2

(0.9%). Diabetes led to the permanent discontinuation of YERVOY with nivolumab in 0.5% and withholding of YERVOY with nivolumab in 0.5% of patients. Systemic corticosteroids were required in 7% (1/15) of patients with diabetes. Diabetes resolved in 27% of the 15 patients. Of the 3 patients in whom YERVOY or nivolumab was withheld for diabetes, 2 received additional treatment after symptom improvement; of these, none had recurrence of diabetes.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Hypophysitis:

Hypophysitis occurred in 9% (42/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (2.4%) and Grade 2 (6%) adverse reactions. Hypophysitis led to permanent discontinuation of YERVOY with nivolumab in 0.9% and withholding of treatment 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 YERVOY with nivolumab was withheld for hypophysitis, 9 reinitiated treatment after symptom improvement, and 1 had recurrence of hypophysitis.

Adrenal Insufficiency:

Adrenal insufficiency occurred in 8% (35/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 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 YERVOY with nivolumab in 0.4% of patients and withholding of treatment in 2.0% 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 YERVOY with nivolumab was withheld for adrenal insufficiency, 7 reinitiated treatment after symptom improvement, and all required hormone replacement therapy for their ongoing adrenal insufficiency.

Hypothyroidism:

Hypothyroidism occurred in 20% (91/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (0.4%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to permanent discontinuation of YERVOY with nivolumab in 0.9% of patients and withholding of treatment 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 YERVOY with nivolumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement, and none had recurrence of hypothyroidism.

Hyperthyroidism:

Hyperthyroidism occurred in 9% (42/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (0.9%) and Grade 2 (4.2%) adverse reactions. Hyperthyroidism led to permanent discontinuation of YERVOY with nivolumab in no patients and withholding of treatment 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 YERVOY with nivolumab was withheld for hyperthyroidism, 8 reinitiated treatment after symptom improvement, and 1 had recurrence of hyperthyroidism.

Immune-Mediated Pneumonitis

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated pneumonitis occurred in 3.9% (26/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (1.4%) and Grade 2 (2.6%). Pneumonitis led to permanent discontinuation of YERVOY and nivolumab in 1.8% and withholding of YERVOY and nivolumab in 1.5% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated pneumonitis. Systemic corticosteroids were therefore required in 100% (26/26) of patients with immune-mediated pneumonitis. Approximately 8% required coadministration of another immunosuppressant with corticosteroids. Pneumonitis resolved in 92% of the 26 patients. Of the 10 patients in whom YERVOY or nivolumab was withheld for pneumonitis, 10 received additional treatment after symptom improvement; of these, 4 had recurrence of pneumonitis.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of YERVOY with nivolumab in 5% of patients and withholding of YERVOY with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of YERVOY with nivolumab.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated pneumonitis occurred in 7% (31/456) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC or melanoma, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%). Immune-mediated pneumonitis led to permanent discontinuation or withholding of treatment in 2.9% and 3.9% of patients, respectively.

Systemic corticosteroids were required in 100% of patients with pneumonitis. Pneumonitis resolved in 94% of the patients. Of the 13 patients in whom YERVOY or nivolumab was withheld

for pneumonitis, 13 received additional treatment after symptom improvement, and 4 had recurrence of pneumonitis.

Immune-Mediated Nephritis with Renal Dysfunction

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%). Nephritis with renal dysfunction led to permanent discontinuation of YERVOY and nivolumab in 1.2% and withholding of nivolumab and YERVOY in 1.8% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated nephritis with renal dysfunction. Systemic corticosteroids were therefore required in 100% (27/27) of patients with immune-mediated nephritis with renal dysfunction. Nephritis with renal dysfunction resolved in 67% of the 27 patients. Of the 12 patients in whom YERVOY or nivolumab was withheld for nephritis, 10 received additional treatment after symptom improvement; of these, 4 had recurrence of nephritis.

Other Immune-Mediated Adverse Reactions

Across clinical trials of YERVOY administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome, and solid organ transplant rejection.

5.2 Infusion-Related Reactions

Severe infusion-related reactions can occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (2.3)]*. Infusion-related reactions occurred in 0.6% (3/511) of patients who received single-agent YERVOY 3 mg/kg for the unresectable or metastatic treatment of melanoma. Infusion-related reactions occurred in 5% (33/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or CRC. Infusion-related reactions occurred in 8% (4/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Infusion-related reactions occurred in 12% (37/300) of patients with malignant pleural mesothelioma who received YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks.

5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT.

Follow patients closely for evidence of GVHD and intervene promptly *[see Adverse Reactions (6.2)]*. Consider the benefit versus risks of treatment with YERVOY after allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight) and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Risks Associated When Administered in Combination with Nivolumab

YERVOY is indicated for use in combination with nivolumab for patients with advanced RCC, MSI-H or dMMR mCRC, HCC, and NSCLC. Refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment.

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)]*.

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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the Warnings and Precautions section reflect exposure to YERVOY 3 mg/kg as a single agent (or in combination with an investigational gp100 peptide vaccine) in 511 patients in Study MDX010-20; YERVOY 1 mg/kg administered with nivolumab 3 mg/kg in 1,362 patients in CHECKMATE-214, CHECKMATE-142, CHECKMATE-227, and CHECKMATE-743; YERVOY 3 mg/kg administered with nivolumab 1 mg/kg in 456 patients enrolled in CHECKMATE-067, CHECKMATE-040, and another randomized trial; and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA.

Unresectable or Metastatic Melanoma

The safety of YERVOY was evaluated in 643 previously treated patients with unresectable or metastatic melanoma in Study MDX010-20 *[see Clinical Studies (14.1)]*. Study MDX010-20 excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Patients received YERVOY 3 mg/kg by intravenous infusion for 4 doses as a single agent (n=131), YERVOY with an investigational gp100 peptide vaccine (n=380), or gp100 peptide vaccine as a single agent (n=132). Patients in the trial received a median of 4 doses (range: 1 to 4 doses).

The trial population characteristics were: median age 57 years (range: 19 to 90), 59% male, 94% White, and baseline ECOG performance status 0 (56%).

YERVOY was discontinued for adverse reactions in 10% of patients. Table 4 presents adverse reactions from Study MDX010-20.

Table 4: Selected Adverse Reactions (≥5%) in Patients Receiving YERVOY with a Difference Between Arms of >5% for All Grades and >1% for Grades 3 to 5 Compared to gp100 Peptide Vaccine in Study MDX010-20

Adverse Reactions	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg and gp100 n=380		gp100 n=132	
	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)
General and Administration-Site Conditions						
Fatigue	41	7	34	5	31	3
Gastrointestinal						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Dermatologic						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0

Unresectable or Metastatic Melanoma: In Combination with Nivolumab

The safety of YERVOY, administered with nivolumab 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:

- YERVOY 3 mg/kg by intravenous infusion over 90 minutes with nivolumab 1 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (YERVOY and nivolumab arm; n=313), or
- Nivolumab 3 mg/kg by intravenous infusion every 2 weeks (nivolumab arm; n=313), or
- YERVOY 3 mg/kg by intravenous infusion over 90 minutes every 3 weeks for up to 4 doses (YERVOY arm; n=311).

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

Serious adverse reactions (74%), adverse reactions leading to permanent discontinuation (47%) or to dosing delays (58%), and Grade 3 or 4 adverse reactions (72%) occurred in patients treated with YERVOY and nivolumab.

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

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

Tables 5 and 6 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

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

Adverse Reaction	YERVOY and Nivolumab (n=313)		Nivolumab (n=313)		YERVOY (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	1.0	17	1.6
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	1.0	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 YERVOY with nivolumab:

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

Laboratory Abnormality	YERVOY and Nivolumab		Nivolumab		YERVOY	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry						
Increased ALT	55	16	25	3.0	29	2.7
Hyperglycemia	53	5	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	2.0	23	2.0
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	4.0

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

Adjuvant Treatment of Melanoma

The safety of YERVOY was evaluated in Study E1609, an open-label, multicenter, randomized trial for the adjuvant treatment of patients with completely resected node positive cutaneous melanoma *[see Clinical Studies (14.2)]*. Patients received YERVOY 3 mg/kg intravenously every 3 weeks for 4 doses followed by 3 mg/kg every 12 weeks for up to 4 additional doses, or high-dose interferon-α2b (HDI). Among patients who received YERVOY, 55% were exposed for 6 months or longer and 42% were exposed for greater than 1 year.

Fatal adverse reactions occurred in 1.4% of patients who received YERVOY, including gastric perforation (0.2%), and cardiac arrest (0.2%). Permanent discontinuation of YERVOY due to an adverse reaction occurred in 35% of patients.

The most common adverse reactions (≥20%) in the YERVOY arm were fatigue, diarrhea, rash, pruritus, nausea, and headache. Table 7 summarizes adverse reactions in E1609.

Table 7: Adverse Reactions (>10%) in Patients Receiving YERVOY 3 mg/kg in E1609

Adverse Reaction	YERVOY 3 mg/kg n=516		HDI n=520	
	All Grades (%)	Grade 3 to 4 (%)	All Grades (%)	Grade 3 to 4 (%)
General disorders and administration site conditions				
Fatigue	56	3	87	22
Decreased appetite	14	0.6	53	2.1
Pyrexia	10	0	31	0.8
Gastrointestinal				
Diarrhea	49	10	34	0.8
Nausea	29	1.2	66	4.2
Abdominal Pain	19	1	9	0.4
Vomiting	11	0.6	26	2.3
Colitis	10	8	1	0.4
Dermatologic				
Rash	46	4	18	1
Pruritus	41	2	15	0
Nervous System Disorders				
Headache	25	2	45	3
Endocrine				
Endocrine disorders, other	19	4.1	2	0
Hypothyroidism	11	0.6	10	0.2
Adrenal insufficiency	10	2	0.6	0

Other Clinical Experience

Across clinical studies in which patients received YERVOY as a single agent at doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence <1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Advanced Renal Cell Carcinoma: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in 1082 patients with previously untreated advanced RCC in CHECKMATE-214 *[see Clinical Studies (14.3)]*. Patients received YERVOY 1 mg/kg with nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg every 2 weeks (n=547) or sunitinib 50 mg orally daily for first 4 weeks of each 6-week cycle (n=535). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in YERVOY and nivolumab arm. In this trial, 57% of patients in the YERVOY and nivolumab arm were exposed to treatment for greater than 6 months and 38% of patients were exposed to treatment for greater than 1 year.

Serious adverse reactions occurred in 59% of patients receiving YERVOY with nivolumab. The most frequent serious adverse reactions reported in ≥2% of patients treated with YERVOY and nivolumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

In patients who received YERVOY with nivolumab, study therapy was discontinued for adverse reactions in 31% and delayed for adverse reactions in 54%.

The most common adverse reactions (≥20%) in the YERVOY and nivolumab arm were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 8 summarizes adverse reactions in CHECKMATE-214.

Table 8: Adverse Reactions (>15%) in Patients Receiving YERVOY and Nivolumab in CHECKMATE-214

Adverse Reaction	YERVOY 1 mg/kg and Nivolumab n=547		Sunitinib n=535	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General and Administration Site Conditions				
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	2.0	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				
Musculoskeletal pain[d]	37	4.0	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 9 summarizes the laboratory abnormalities in CHECKMATE-214.

Table 9: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving YERVOY and Nivolumab in CHECKMATE-214

Laboratory Abnormality	YERVOY 1 mg/kg and Nivolumab[a]		Sunitinib[a]	
	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	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3.0	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: nivolumab and YERVOY 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 YERVOY with nivolumab group compared to the sunitinib group (31% and 61%, respectively).

MSI-H or dMMR Metastatic Colorectal Cancer

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

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-8HW, a randomized, open-label, three arm trial in immunotherapy naïve patients with MSI-H or dMMR mCRC *[see Clinical Studies (14.4)]*. Patients received one of the following:

- YERVOY 1 mg/kg every 3 weeks and nivolumab 240 mg every 3 weeks for a maximum of 4 doses, then nivolumab 480 mg every 4 weeks.
- Nivolumab 240 mg every 2 weeks for 6 doses, then nivolumab 480 mg every 4 weeks.
- Investigator's choice chemotherapy: mFOLFOX or FOLFIRI *[see Clinical Studies (14.4)]*.

In the YERVOY and nivolumab arm, the median duration of exposure to YERVOY was 2.1 months (range 1 day to 3.7 months); patients received a median of 4 doses (range 1-4). The median duration of treatment in the YERVOY and nivolumab arm was 20.5 months (range: 1 day to 35.9 months); 70% were exposed to treatment for >6 months, and 63% were exposed for >1 year. The

median duration of treatment was 16.4 months (range: 1 day to 36 months) in the nivolumab-only arm; 64% were exposed to treatment for >6 months, and 54% were exposed for >1 year.

Serious adverse reactions occurred in 46% of patients receiving YERVOY in combination with nivolumab, and 39% of patients receiving nivolumab alone. The most frequent serious adverse reactions reported in ≥1% of patients who received YERVOY with nivolumab 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 YERVOY in combination with nivolumab; these included myocarditis, and pneumonitis (1 each).

YERVOY and/or nivolumab 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%). Nivolumab was permanently discontinued in 13% of patients receiving single agent nivolumab. Adverse reactions leading to the delay of YERVOY and/or nivolumab occurred in 48% of patients receiving the combination; single agent nivolumab was delayed in 37% of patients due to adverse reactions.

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

Tables 10 and 11 summarize the adverse reactions and selected laboratory abnormalities, for YERVOY in combination with nivolumab and nivolumab arms respectively, in CHECKMATE-8HW.

Table 10: Adverse Reactions in ≥10% in Patient and a Difference Between Arms of >5% for All Grades in - CHECKMATE-8HW

Adverse Reaction	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				
Diarrhea[a]	35	4.5	30	3.4
Skin and Subcutaneous Tissue				
Pruritus	30	0	23	0
Musculoskeletal and Connective Tissue				

Table 10: Adverse Reactions in ≥10% in Patient and a Difference Between Arms of >5% for All Grades in - CHECKMATE-8HW

Adverse Reaction	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Arthralgia	20	0.6	15	0.6
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 11: 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]	YERVOY and Nivolumab (n=352)		Nivolumab (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: YERVOY and nivolumab group (range: 108 to 343 patients) or nivolumab group (range: 102 to 348 patients).

Hepatocellular Carcinoma: In Combination with Nivolumab

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-9DW, a randomized, open-label trial in adult patients with unresectable or metastatic HCC *[see Clinical Studies (14.5)]*. Patients received YERVOY in combination with nivolumab (n=332) or investigator's choice of lenvatinib (n=275) or sorafenib (n=50) at the following dosage:

- YERVOY 3 mg/kg administered intravenously over 30 minutes in combination with nivolumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent nivolumab 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 YERVOY and nivolumab arm, the median duration of exposure to nivolumab 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 YERVOY in combination with nivolumab. The most frequent non-liver-related serious adverse reactions reported in ≥2% were diarrhea/colitis (4.5%), gastrointestinal hemorrhage (3%), and rash (2.4%).

Liver-related serious adverse reactions occurred in 17% of patients treated with YERVOY in combination with nivolumab, 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 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 YERVOY in combination with nivolumab; 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 discontinuation due to an adverse reaction occurred in 27% of patients treated with YERVOY in combination with nivolumab. Adverse reactions leading to permanent discontinuation in >1% of patients included immune-mediated hepatitis (1.8%), diarrhea/colitis (1.8%), and hepatic failure (1.2%).

Dosage interruptions due to an adverse reaction occurred in 62% of patients treated with YERVOY in combination with nivolumab. 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 12 and 13 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9DW.

Table 12: Adverse Reactions Occurring in ≥10% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	YERVOY and Nivolumab (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 12: Adverse Reactions Occurring in ≥10% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	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 YERVOY with nivolumab were hyperglycemia (8%), adrenal insufficiency (4.2%), pneumonitis (2.7%), and pancreatitis (2.4%).

Table 13: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	YERVOY and Nivolumab (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
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

Table 13: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
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: YERVOY and nivolumab group (range: 168 to 331 patients) and lenvatinib or sorafenib group (range: 145 to 315 patients).

Previously Treated Hepatocellular Carcinoma

The safety of YERVOY 3 mg/kg in combination with nivolumab 1 mg/kg was evaluated in a subgroup of 49 patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib enrolled in Cohort 4 of CHECKMATE-040. YERVOY and nivolumab were administered every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

During the YERVOY and nivolumab combination period, 33 of 49 (67%) patients received all four planned doses of YERVOY and nivolumab. During the entire treatment period, the median duration of exposure to YERVOY was 2.1 months (range: 0 to 4.5 months) and to nivolumab was 5.1 months (range: 0 to 35+ 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.

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.

Table 14 summarizes the adverse reactions and Table 15 summarizes the laboratory abnormalities of YERVOY in combination with nivolumab in CHECKMATE-040.

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (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		

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
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
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 receiving YERVOY with nivolumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Table 15: Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Laboratory Abnormality	YERVOY and Nivolumab (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 YERVOY with nivolumab, 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.

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

The safety of YERVOY in combination with nivolumab 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 (14.6)]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received YERVOY 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks and nivolumab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in YERVOY and nivolumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received YERVOY and nivolumab for >6 months and 23% of patients received YERVOY and nivolumab 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. YERVOY and nivolumab 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 16 and 17 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 16: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (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
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	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	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	4.0

Table 16: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
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 generalized, 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 17: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY and Nivolumab - CHECKMATE-227

Laboratory Abnormality	YERVOY and Nivolumab		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
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: YERVOY and nivolumab 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 Nivolumab and Platinum-Doublet Chemotherapy

The safety of YERVOY in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.6)]*. Patients received either YERVOY 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 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 YERVOY in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received YERVOY and nivolumab for >6 months and 13% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with YERVOY in combination with nivolumab 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 YERVOY in combination with nivolumab 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 18 and 19 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 18: Adverse Reactions in >10% of Patients Receiving YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	YERVOY and Nivolumab 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	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	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	2.0	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 19: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	YERVOY and Nivolumab 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
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: YERVOY and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

First-line Treatment of Unresectable Malignant Pleural Mesothelioma: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-743, a randomized, open-label trial in patients with previously untreated unresectable malignant pleural mesothelioma *[see Clinical Studies (14.7)]*. Patients received either YERVOY 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks and nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks for up to 2 years; or platinum-doublet chemotherapy for up to 6 cycles. The median duration of therapy in YERVOY and nivolumab-treated patients was 5.6 months (range: 0 to 26.2 months); 48% of patients received YERVOY and nivolumab for >6 months and 24% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 54% of patients who were treated with YERVOY in combination with nivolumab. 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 YERVOY and nivolumab were permanently discontinued due to adverse reactions in 23% of patients and 52% had at least one dose withheld due to an adverse reaction. An additional 4.7% of patients permanently discontinued YERVOY alone due to adverse reactions.

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

Tables 20 and 21 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-743.

Table 20: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-743

Adverse Reaction	YERVOY and Nivolumab (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	1.0	1.1	0
Skin and Subcutaneous Tissue				
Rash[e]	34	2.7	11	0.4
Pruritus[f]	21	1.0	1.4	0
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	1.0	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	4.0	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 21: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY and Nivolumab - CHECKMATE-743

Laboratory Abnormality	YERVOY and Nivolumab		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: YERVOY and nivolumab group (range: 109 to 297 patients) and chemotherapy group (range: 90 to 276 patients).

First-line Treatment of Unresectable Advanced or Metastatic ESCC: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab 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 (14.8)]*. Patients received one of the following treatments:

- YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 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 YERVOY and nivolumab, the median duration of exposure was 2.8 months (range: 0 to 24 months).

Serious adverse reactions occurred in 69% of patients receiving YERVOY in combination with nivolumab.

The most frequent serious adverse reactions reported in ≥2% of patients who received YERVOY with nivolumab were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), 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 YERVOY in combination with nivolumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

YERVOY and/or nivolumab were discontinued in 23% of patients and delayed in 46% of patients for an adverse reaction.

The most common adverse reactions reported in ≥20% of patients treated with YERVOY in combination with nivolumab were rash, fatigue, pyrexia, nausea, diarrhea, and constipation.

Tables 22 and 23 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-648.

Table 22: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-648

Adverse Reaction	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	31	3.1	7	0
Pruritis	17	0.9	3.6	0
General				
Fatigue[c]	28	2.5	41	4.9
Pyrexia[b]	23	0.9	12	0.3
Gastrointestinal				
Nausea	22	0.6	56	2.6
Diarrhea	22	1.9	20	2.0
Constipation	20	0.3	43	1.0
Vomiting	15	1.6	19	3.0
Dysphagia	12	5	12	4.9
Stomatitis[d]	11	0.6	35	3.0

Table 22: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-648

Adverse Reaction	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Abdominal pain[e]	10	0.9	11	0.7
Metabolism and Nutrition				
Decreased appetite	17	4.0	50	6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[f]	14	0.6	8	0.3
Infections and Infestations				
Pneumonia[g]	14	8	10	2.6
Endocrine				
Hypothyroidism	14	0	0.3	0
Respiratory, Thoracic and Mediastinal				
Cough[h]	13	0.3	13	0.3
Investigations				
Weight decreased	12	1.9	11	1.0

Toxicity was graded per NCI CTCAE v4.

[a] 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.

[b] Includes tumor associated fever.

[c] Includes asthenia and malaise.

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

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

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

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

[h] Includes productive cough.

Table 23: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients on YERVOY and Nivolumab - CHECKMATE-648

Laboratory Abnormality	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	52	7	66	14
Lymphopenia	50	13	44	8
Neutropenia	13	1.3	48	13
Thrombocytopenia	12	1.0	29	2.8
Chemistry				
Hyponatremia	45	11	40	8
Hyperglycemia	43	4.3	36	0.8
Increased AST	39	6	11	1.4
Increased ALT	33	6	8	0.7
Hypocalcemia	32	0	23	0.7

Table 23: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients on YERVOY and Nivolumab - CHECKMATE-648

Laboratory Abnormality	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increased alkaline phosphatase	31	3.3	15	0
Hyperkalemia	23	1.6	24	0.7
Hypokalemia	19	5	17	6
Hypercalcemia	15	2.0	8	0
Hypoglycemia	15	1.2	7	0
Increased creatinine	15	0.7	31	0.7
Hypomagnesemia	15	0	25	1.8

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of YERVOY. 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.

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

Immune System: graft-versus-host disease, solid organ transplant rejection

Skin and Subcutaneous Tissue: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, YERVOY can cause fetal harm when administered to a pregnant woman. There is insufficient human data for YERVOY exposure in pregnant women. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner *(see Data)*. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Bristol-Myers Squibb at 1-844-593-7869.

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

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the humans exposure based on area under the curve at a dose of 3 mg/kg). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/−), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/− heterozygous offspring. Mated CTLA-4+/− heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4−/−). The CTLA-4−/− homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

8.2 Lactation

Risk Summary

There are no data on the presence of YERVOY in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with YERVOY and for 3 months following the last dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

YERVOY 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 YERVOY and for 3 months following the last dose.

8.4 Pediatric Use

The safety and effectiveness of YERVOY have been established in pediatric patients aged 12 years and older for the following indications: as a single agent and in combination with nivolumab for unresectable or metastatic melanoma, in combination with nivolumab for the treatment of MSI-H or dMMR unresectable and metastatic CRC, and in combination with nivolumab for MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY 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. Ipilimumab exposures in pediatric patients 12 years and older are 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 (14.4)]*.

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

The safety and effectiveness of YERVOY have not been established in pediatric patients for the adjuvant treatment of melanoma or for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, metastatic non-small cell lung cancer, malignant pleural mesothelioma and esophageal cancer.

In a dose-finding trial (NCT01445379), 33 patients aged 2 to 21 years (median 13 years) with relapsed or refractory solid tumors were evaluated including unresectable stage IIIc or stage IV melanoma (12), progressive or refractory sarcomas (17), renal or bladder carcinoma (3), and neuroblastoma (1). No responses in the patients with non-melanoma solid tumors and no new safety signals were observed in pediatric patients in this study.

8.5 Geriatric Use

Single Agent

Of the 511 patients treated with YERVOY in Study MDX010-20 (unresectable or metastatic melanoma), 28% were 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

In Combination with Nivolumab

Of the 314 patients randomized to YERVOY administered with nivolumab in CHECKMATE-067, 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.

Of the 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 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 YERVOY with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to YERVOY

1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227, 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 (14.6)]*.

Of the 303 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-743 (malignant pleural mesothelioma), 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 rate due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received YERVOY with nivolumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and discontinuation 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 YERVOY in combination with nivolumab.

Of the 550 patients randomized to YERVOY 1 mg/kg with nivolumab in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.

Of the 354 patients with dMMR or MSI-H metastatic CRC (mCRC) who were randomized to YERVOY in combination with nivolumab, 44% were 65 years or older and 14% were 75 years or older. Of the 353 patients randomized to nivolumab, 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 YERVOY in combination with nivolumab compared to those younger than 65 receiving the combination (42%). There was a higher incidence of adverse reactions leading to discontinuation in patients aged 65 years or older receiving YERVOY in combination with nivolumab (23%) compared to those younger than 65 receiving the combination (15%). No overall differences in effectiveness were reported between elderly patients and younger patients receiving YERVOY in combination with nivolumab *[see Clinical Studies (14.4)]*.

Of the 335 patients with unresectable hepatocellular carcinoma who were randomized to YERVOY in combination with nivolumab, 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.

Of the 49 patients who received YERVOY 3 mg/kg with nivolumab in Cohort 4 of CHECKMATE-040 (previously treated hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of YERVOY in combination with nivolumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

Of the 325 patients who received YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-648 (ESCC), 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 YERVOY with nivolumab (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.

Study CA184-029 (adjuvant treatment of melanoma) and CHECKMATE-142 (metastatic colorectal cancer) did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

In Combination with Nivolumab and Platinum-Doublet Chemotherapy

Of the 361 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 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 YERVOY with nivolumab 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 YERVOY in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, 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.

11 DESCRIPTION

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. Ipilimumab is a recombinant IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

YERVOY (ipilimumab) injection, for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-dose vials of 50 mg/10 mL or 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation

and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 mg/kg to 10 mg/kg. Following administration of YERVOY every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean minimum concentration (C_{min}) at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks.

Elimination

The mean (percent coefficient of variation) terminal half-life ($t_{1/2}$) was 15.4 days (34%) and then mean (percent coefficient of variation) clearance (CL) was 16.8 mL/h (38%).

The CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations

The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment (glomerular filtration rate ≥15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] >1 to 1.5 times the upper limit of normal [ULN] or AST > ULN), previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-White racial groups. YERVOY has not been studied in patients with moderate (TB >1.5 to 3 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

Pediatric Patients

The exposures of ipilimumab in pediatric patients 12 years and older are comparable to those in adult patients at the recommended dosage.

Drug Interaction Studies

Ipilimumab with Nivolumab

When YERVOY 1 mg/kg was administered with nivolumab 3 mg/kg every 3 weeks, the CL of ipilimumab was unchanged compared to when YERVOY was administered alone.

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

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

administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

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

12.6 Immunogenicity

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

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay had substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Seven (4.9%) of 144 patients receiving ipilimumab developed anti-ipilimumab antibodies and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for anti-ipilimumab antibodies using an ECL assay with improved drug tolerance. No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for anti-ipilimumab antibodies.

Of the 499 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-214 and CHECKMATE-142, 27 (5.4%) were positive for anti-ipilimumab antibodies; there were no patients with neutralizing antibodies against ipilimumab. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies.

Of 483 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part 1, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, of 491 patients evaluable for anti-nivolumab antibodies, 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

Of 271 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-743, 13.7% were positive for anti-ipilimumab antibodies and 0.4% were positive for anti-ipilimumab neutralizing antibodies. Of 269 patients evaluable for anti-nivolumab antibodies in CHECKMATE-743, 25.7% were positive for anti-nivolumab antibodies and 0.7% had neutralizing antibodies against nivolumab.

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 24.

Table 24: YERVOY Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Incidence

Treatment Regimen[a]	Indication(s)	ADA	NAb[b]
YERVOY as a single agent	Melanoma	1.1% (11/1024)	0 (0/11)
	Adjuvant Melanoma	4.9 (7/144)	0 (0/7)
YERVOY with nivolumab for 4 doses followed by nivolumab as a single agent	Melanoma	8.4% (33/391)	3% (1/33)
	HCC	5.3% (13/244)	0 (0/13)
	RCC and CRC	5.4% (27/499)	0% (0/27)
YERVOY with nivolumab	Malignant Pleural Mesothelioma	13.7% (37/271)	2.7% (1/37)
	NSCLC	8.5% (41/483)	0 (0/41)
YERVOY with nivolumab and 2 cycles of platinum-doublet chemotherapy	NSCLC	7.5% (23/305)	21.7% (5/23)

[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.

ADA = treatment-emergent anti-ipilimumab 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-ipilimumab antibodies did not affect ipilimumab clearance after administration of ipilimumab as monotherapy or in combination with nivolumab. 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. In hepatocellular carcinoma, there was no identified clinically significant effect of anti-drug antibodies on efficacy for ipilimumab in combination with nivolumab. For other indications, the effects of anti-drug antibodies on effectiveness have not been fully characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies, and the genotoxic potential of ipilimumab has not been evaluated.

Fertility studies have not been performed with ipilimumab.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The efficacy of YERVOY was investigated in a Study MDX010-20, a randomized (3:1:1), double-blind, double-dummy trial (NCT00094653) that included patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. The trial enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Patients were randomized to YERVOY administered at a dose of 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses with an investigational peptide vaccine with incomplete Freund's adjuvant - gp100 administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for 4 doses; gp100 administered at a dose of 2 mg by deep subcutaneous injection every 3 weeks for 4 doses as a single agent with a placebo; or YERVOY administered at a dose of 3 mg/kg by intravenous infusion every 3 weeks for 4 doses with a placebo. The major efficacy outcome measure was overall survival (OS) in the YERVOY and gp100 arm compared to that in the single-agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY and gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) as assessed by the investigator at week 24 between each of the trial arms, and duration of response. Assessment of tumor response was conducted at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

A total of 676 patients were randomized, 403 to YERVOY and gp100 arm, 137 to YERVOY single agent arm and 136 to gp100 single agent arm. Of the randomized patients, 61%, 59%, and 54% in the YERVOY and gp100, YERVOY, and gp100 arms, respectively, were male. Twenty-nine percent were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin, and 38% had elevated LDH level. Sixty-one percent of patients randomized to either YERVOY-containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

The efficacy results are shown in Table 25 and Figure 1.

Table 25: Efficacy Results for Study MDX010-20

	YERVOY 3 mg/kg n=137	**YERVOY 3 mg/kg and gp100 n=403**	**gp100 n=136**
Overall Survival			
Median in months (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)
Hazard ratio (vs. gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p=0.0026[a]	p=0.0004	

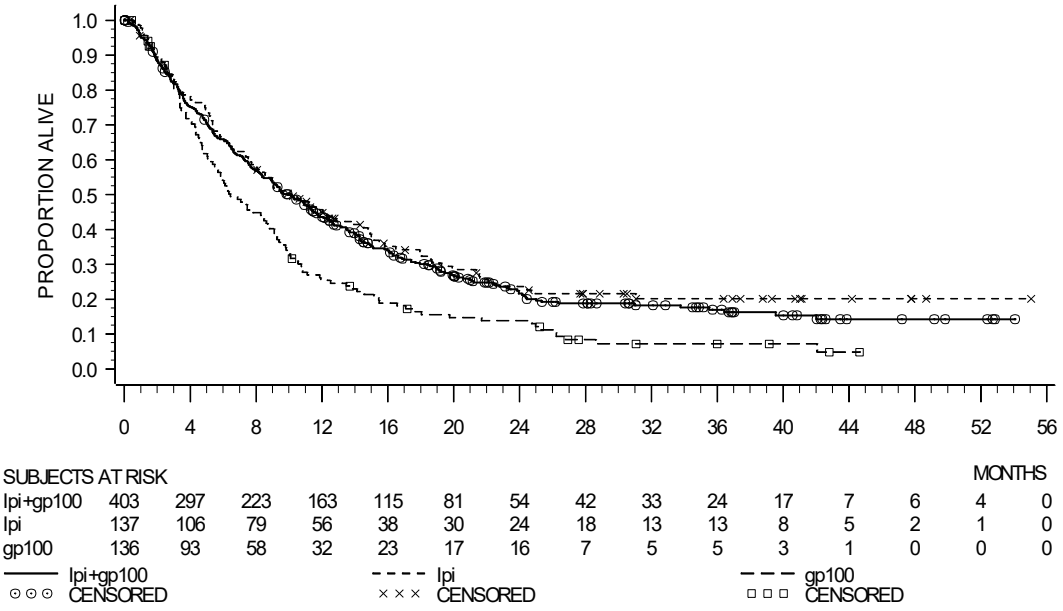
Table 25: Efficacy Results for Study MDX010-20

	YERVOY 3 mg/kg n=137	YERVOY 3 mg/kg and gp100 n=403	gp100 n=136
Hazard ratio (vs. YERVOY) (95% CI)		1.04 (0.83, 1.30)	
Best Overall Response Rate (BORR) (95% CI)	10.9% (6.3%, 17.4%)	5.7% (3.7%, 8.4%)	1.5% (0.2%, 5.2%)
Median duration of response in months	NR[b]	11.5	NR[b]

[a] Not adjusted for multiple comparisons.

[b] Not Reached

Figure 1: Kaplan-Meier Curves for Overall Survival in Study MDX010-20



Previously Untreated Metastatic Melanoma: In Combination with Nivolumab

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in which 945 patients with previously untreated, unresectable or metastatic melanoma were randomized to one of the following arms: YERVOY and nivolumab, nivolumab, or YERVOY. 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:

- YERVOY 3 mg/kg with nivolumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (YERVOY and nivolumab arm),
- Nivolumab 3 mg/kg by intravenous infusion every 2 weeks (nivolumab arm), or
- YERVOY 3 mg/kg intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks (YERVOY 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 nivolumab-containing arm as compared with the YERVOY arm. The trial was not designed to assess whether adding YERVOY to nivolumab improves PFS or OS compared to nivolumab as a single agent. Efficacy results are shown in Table 26 and Figure 2.

Table 26: Efficacy Results - CHECKMATE-067

	YERVOY and Nivolumab (n=314)	**Nivolumab (n=316)**	**YERVOY (n=315)**
Overall Survival[a]			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio[b] (vs. YERVOY) (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. YERVOY) (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			

Table 26: Efficacy Results - CHECKMATE-067

	YERVOY and Nivolumab (n=314)	Nivolumab (n=316)	YERVOY (n=315)
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.

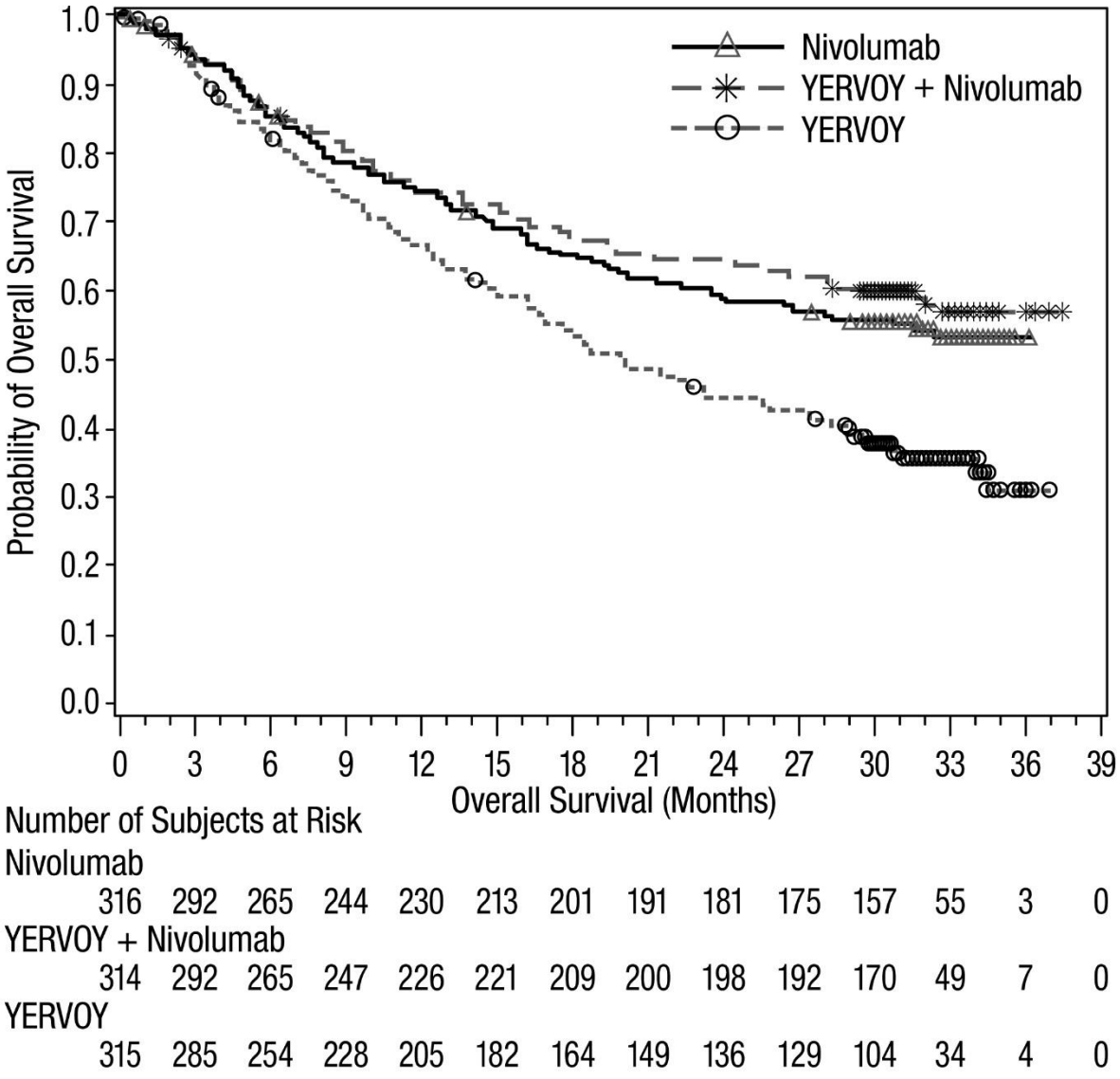
[d] If the maximum of the two OS p-values is less than 0.04 (a significance level assigned by the Hochberg procedure), then both p-values are considered significant.

[e] p-value is compared with 0.005 of the allocated alpha for final PFS treatment comparisons.

[f] Based on the stratified Cochran-Mantel-Haenszel test.

+ Censored observation

Figure 2: 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 YERVOY and nivolumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the nivolumab arm and 19.9 months (95% CI: 16.9, 24.6) in the YERVOY 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 YERVOY and nivolumab arm, 6.9 months (95% CI: 4.3, 9.5) in the nivolumab arm, and 2.9 months (95% CI: 2.8, 3.2) in the YERVOY arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥24 months was 55% in the YERVOY and nivolumab arm, 56% in the nivolumab arm, and 39% in the YERVOY arm.

14.2 Adjuvant Treatment of Melanoma

The efficacy of YERVOY was evaluated in Study E1609 (NCT01274338), an open-label, multicenter, randomized trial for the adjuvant treatment of cutaneous melanoma in patients with completely resected node positive disease (either clinically detectable or any size with ulceration or mitosis $\geq 1/mm^2$), in transit metastasis, satellites, or metastatic disease. The trial excluded patients with a history of prior therapy for melanoma and autoimmune disease requiring steroid treatment. Patients were randomized to receive one of the following regimens:

- YERVOY 3 mg/kg intravenously every 3 weeks for 4 doses, followed by the same dose every 12 weeks for up to 4 additional doses,
- High-dose interferon α-2b (HDI) intravenously at 20 million units/m^2 per day, 5 days per week, for 4 weeks (induction), followed by 10 million units/m^2 per day SC every other day, 3 days per week, for 48 weeks (maintenance), or
- YERVOY 10 mg/kg intravenously every 3 weeks for 4 doses, followed by the same dose every 12 weeks for up to 4 additional doses.

Randomization was stratified by AJCC 7th edition stage (IIIB, IIIC, M1a, or M1b). Tumor assessments were conducted every 3 months in patients <2 years from study entry, then every 6 months in patients 2-5 years from study entry, and every 12 months in patients >5 years from study entry for up to 20 years. Treatment continued for a maximum of 60 weeks with ipilimumab or 52 weeks with HDI, or until unacceptable toxic effects, disease progression, or withdrawal of consent. The major efficacy outcome measures were investigator-assessed recurrence-free survival (RFS) by imaging (for CNS lesions) or imaging and positive cytology or histology (for non-CNS lesions) and overall survival (OS). Only the efficacy results for the recommended starting dose of 3 mg/kg YERVOY are described below.

A total of 1051 patients were randomized to YERVOY 3 mg/kg (n=523) and HDI (n=528). The median age was 54 years (range: 18 to 83), 62% were male, 97% were white, 0.3% were Asian, and 0.4% were Black. Regarding disease stage, 53% had Stage IIIB, 40% had Stage IIIC (with no in-transit metastases), and 7% had Stage IV disease.

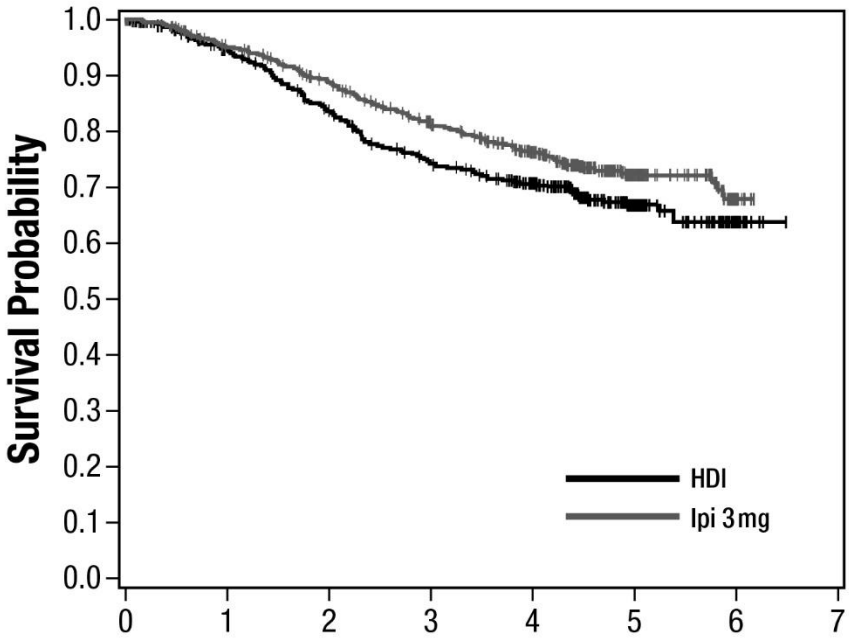
The efficacy results are in Table 27 and Figure 3.

Table 27: Efficacy Results for E1609

	YERVOY 3 mg/kg n=523	**HDI n=528**
Overall Survival		
Number of deaths (%)	130 (25)	134 (25)
Hazard ratio (95% CI)	0.78 (0.61, 0.99)	
p-value (stratified log-rank[a])	0.044	
5-year OS Rates (95% CI)	72 (68, 76)	67 (62, 71)
Recurrence-Free Survival		
Number of events (%)	246 (47)	232 (44)
Median in years (95% CI)	4.5 (2.7, NA)	2.5 (1.8, 3.5)
Hazard ratio (95% CI)	0.85 (0.71, 1.02)	

[a] Two-sided p-value from log-rank test stratified by AJCC stage.

Figure 3: Kaplan-Meier Curves for Overall Survival with Ipilimumab 3 mg/kg vs. HDI in Study E1609



Time Interval							
Treatment	0-1	1-2	2-3	3-4	4-5	5-6	6-7
HDI	528	393	343	297	252	103	16
Ipi 3mg	523	475	429	380	309	114	17

(Number at Risk)

14.3 Advanced Renal Cell Carcinoma

The efficacy of YERVOY with nivolumab was evaluated in CHECKMATE-214 (NCT02231749), a randomized (1:1), open-label study 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 randomized to nivolumab 3 mg/kg and YERVOY 1 mg/kg administered intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every two weeks or to sunitinib administered orally 50 mg daily for the first 4 weeks of each 6-week cycle. Treatment continued until disease progression or unacceptable toxicity. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. Intermediate/poor risk

patients had at least 1 or more of 6 prognostic risk factors as per the IMDC criteria: less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status (KPS) <80%, hemoglobin less than the lower limit of normal, corrected calcium >10 mg/dL, platelet count >ULN, and absolute neutrophil count >ULN.

A total of 847 patients were randomized, 425 to YERVOY with nivolumab and 422 to sunitinib. The 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.

Efficacy results from CHECKMATE-214 are presented in Table 28 and Figure 4. In intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to YERVOY and nivolumab arm as compared with sunitinib arm. OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

Table 28: Efficacy Results for CHECKMATE-214

Efficacy Parameter	**Intermediate/Poor-Risk**	
	YERVOY 1 mg/kg and Nivolumab n=425	**Sunitinib n=422**
Overall Survival		
Number of deaths	140 (32.9%)	188 (44.5%)
Median in months	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9%, 46.5%)	26.5% (22.4%, 31.0%)
Complete Response	40 (9.4%)	5 (1.2%)
Partial Response	137 (32.2%)	107 (25.4%)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
p-value[d,e]	<0.0001	
Progression-free Survival		
Number of events (progression or death)	228 (53.6%)	228 (54.0%)
Median in months	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.

[b] Based on a stratified log-rank test.

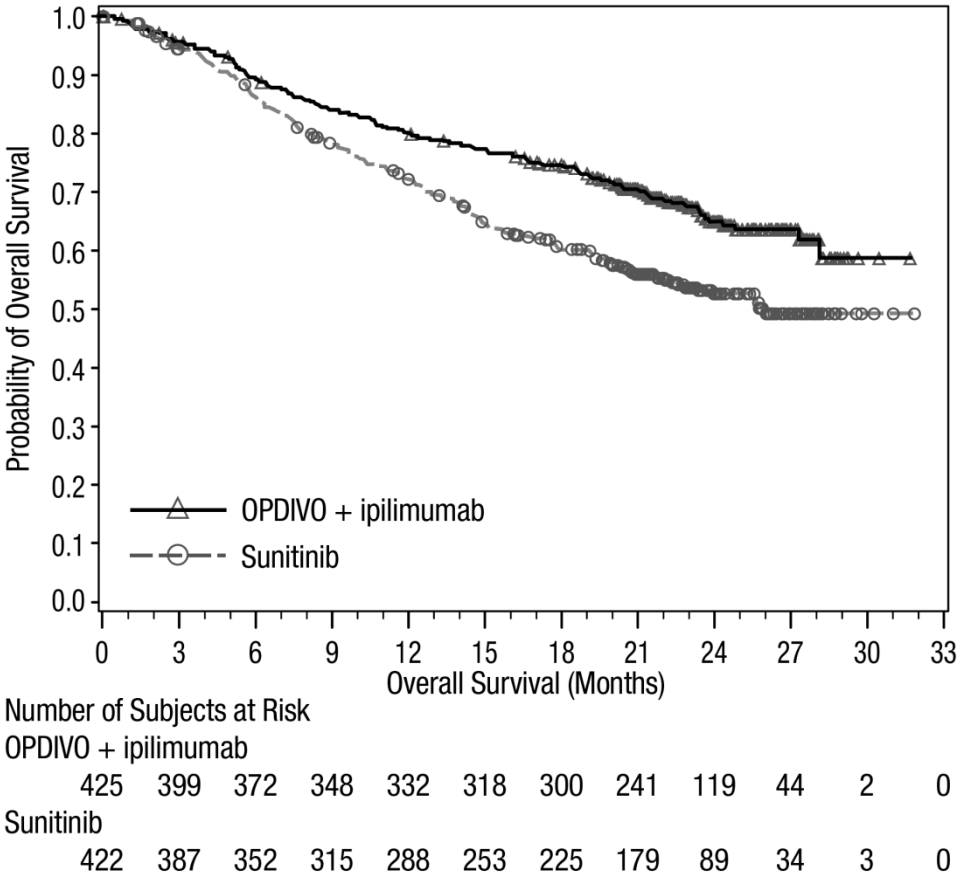
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.

[d] Based on the stratified DerSimonian-Laird test.

[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.

[f] Not Significant at alpha level of 0.009.

Figure 4: Kaplan-Meier Curves for Overall Survival (Intermediate/Poor Risk Population) in CHECKMATE-214



CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab and YERVOY (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 nivolumab and YERVOY compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab and YERVOY in previously untreated renal cell carcinoma with favorable risk disease has not been established.

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

Treatment of MSI-H or dMMR mCRC In Combination with Nivolumab

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:

- YERVOY 1 mg/kg every 3 weeks and nivolumab 240 mg every 3 weeks for a maximum of 4 doses, then nivolumab 480 mg every 4 weeks
- Nivolumab 240 mg every 2 weeks for 6 doses, then nivolumab 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 YERVOY plus nivolumab combination upon progression assessed by BICR.

Study treatment was administered until disease progression, unacceptable toxicity, or for up to 2 years for patients who received YERVOY plus nivolumab or nivolumab monotherapy. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent. Nivolumab with or without YERVOY 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 YERVOY in combination with nivolumab versus chemotherapy in the first-line (1L) setting and the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to YERVOY in combination with nivolumab vs nivolumab in all lines setting.

The major efficacy outcome measure was BICR-assessed PFS per RECIST 1.1. Additional efficacy 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 (48%); number of prior lines of therapy was 0 (56%) and 1

(24%), and ≥2 (19%); 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 all randomized patients.

First Line YERVOY in combination with nivolumab

Among 303 patients in the first-line setting were randomly assigned to YERVOY in combination with nivolumab (202) and to chemotherapy (101), 171 and 84 patients had centrally confirmed MSI-H/dMMR status in YERVOY in combination with nivolumab arm and chemotherapy arm, respectively.

In the 1L setting, 200 of 202 patients assigned to receive YERVOY in combination with nivolumab and 88 of 101 patients assigned to received 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 YERVOY and nivolumab arm compared with chemotherapy in the 1L setting are presented in Table 29 and Figure 5. 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 29: Efficacy Results - CHECKMATE-8HW

	YERVOY and Nivolumab (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.

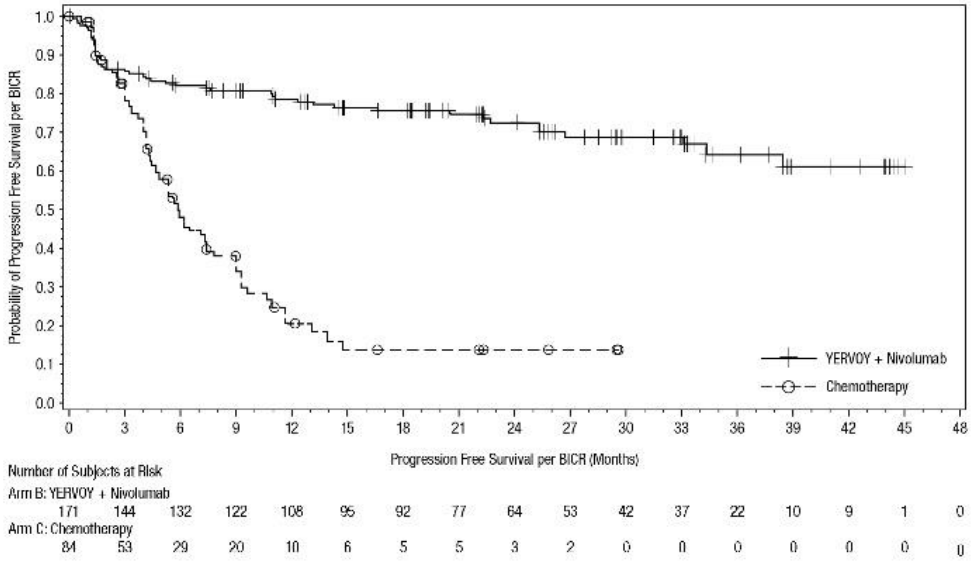
Minimum follow-up was 6.1 months at data cutoff date 12Oct2023.

[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 5: Progression-free Survival, (First line YERVOY + nivolumab vs Chemotherapy)- CHECKMATE-8HW



All Lines YERVOY in combination with nivolumab

Among 707 patients across all treatment lines who were randomly assigned to YERVOY in combination with nivolumab (354) and to nivolumab (353) single agent, 296 and 286 patients had centrally confirmed MSI-H/dMMR status in the YERVOY in combination with nivolumab arm and in the nivolumab 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 YERVOY in combination with nivolumab compared with nivolumab single agent across all treatment lines setting are presented in Table 30 and Figure 6. At the time of PFS analysis OS between arms were not available due to statistical testing strategy.

Table 30: Efficacy Results All Lines - CHECKMATE-8HW

	YERVOY and Nivolumab (n=296)	**Nivolumab (n=286)**
Progression-free Survival		
Disease progression or death n (%)	101 (34)	136 (48)
Median (months)[b] (95% CI)	NR (53.82, 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, n (%)	119 (40%)	65 (30%)

Table 30: Efficacy Results All Lines - CHECKMATE-8HW

	YERVOY and Nivolumab (n=296)	Nivolumab (n=286)
p-value[d]	0.0011	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 16.7 months at data cutoff date 28Aug2024.

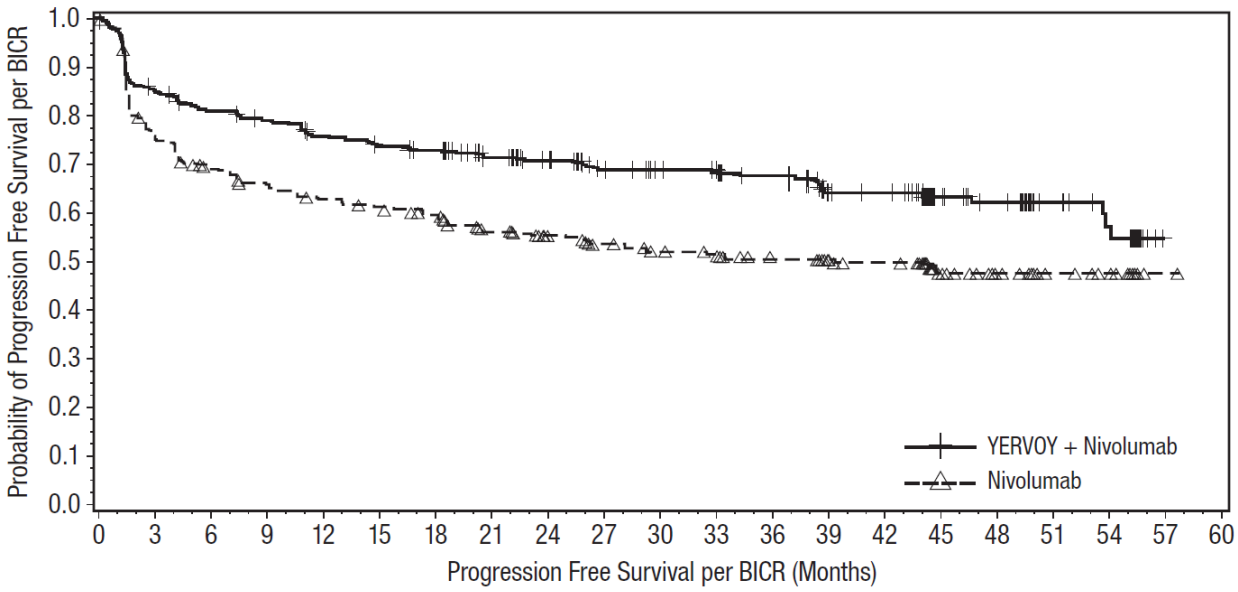
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0095.

[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 6: Progression-free Survival (All lines (YERVOY + Nivolumab vs Nivolumab)- CHECKMATE-8HW



14.5 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:

- YERVOY 3 mg/kg administered intravenously over 30 minutes in combination with nivolumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent nivolumab 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 YERVOY in combination with nivolumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab 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 YERVOY in combination with nivolumab (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 was 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 31 and Figure 7.

Table 31: Efficacy Results - CHECKMATE-9DW

	YERVOY and Nivolumab (n=335)	Lenvatinib or Sorafenib (n=333)
Overall Survival		
Deaths (%)	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (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

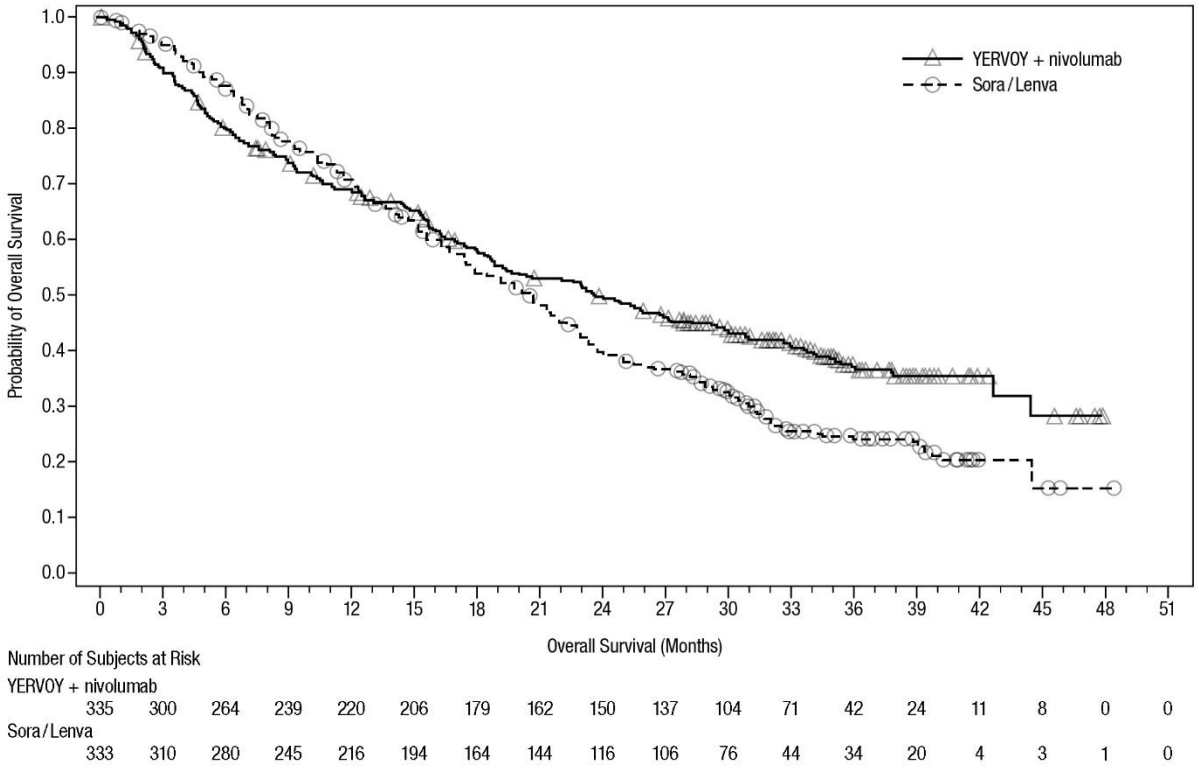
[c] Assessed by BICR using RECIST 1.1

[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 7: Overall Survival - CHECKMATE-9DW



Previously Treated Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial conducted in patients with 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.

The efficacy of YERVOY 3 mg/kg in combination with nivolumab 1 mg/kg was evaluated in Cohort 4 of CHECKMATE-040. A total of 49 patients received the combination regimen, which was administered every 3 weeks for four doses, followed by single-agent nivolumab 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 percent (57%) 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 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 alfa-fetoprotein (AFP) levels ≥400 µg/L. Prior 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 32.

Table 32: Efficacy Results - Cohort 4 of CHECKMATE-040

	YERVOY and Nivolumab (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.

14.6 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab

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 [ASLC] 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:

- YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 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 YERVOY were permitted to continue nivolumab 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 YERVOY in combination with nivolumab (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 YERVOY and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 33 and Figure 8.

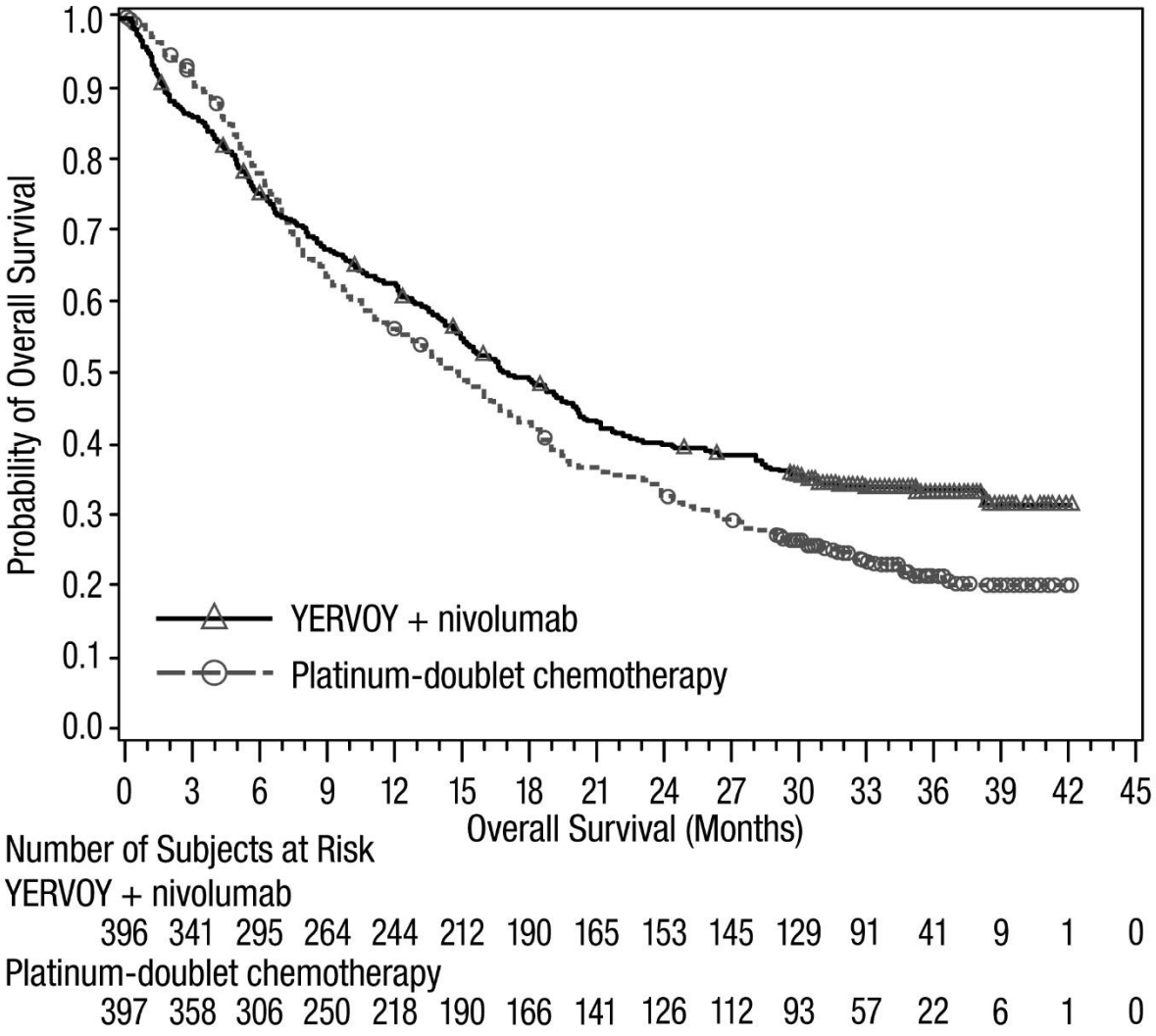
Table 33: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	YERVOY and Nivolumab (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 YERVOY and nivolumab 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 YERVOY and nivolumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the YERVOY and nivolumab 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 Nivolumab 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:

- YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks, nivolumab 360 mg administered intravenously over 30 minutes every 3 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 YERVOY were permitted to continue nivolumab 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 YERVOY in combination with nivolumab 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 34.

Table 34: Efficacy Results - CHECKMATE-9LA

	YERVOY and Nivolumab 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.

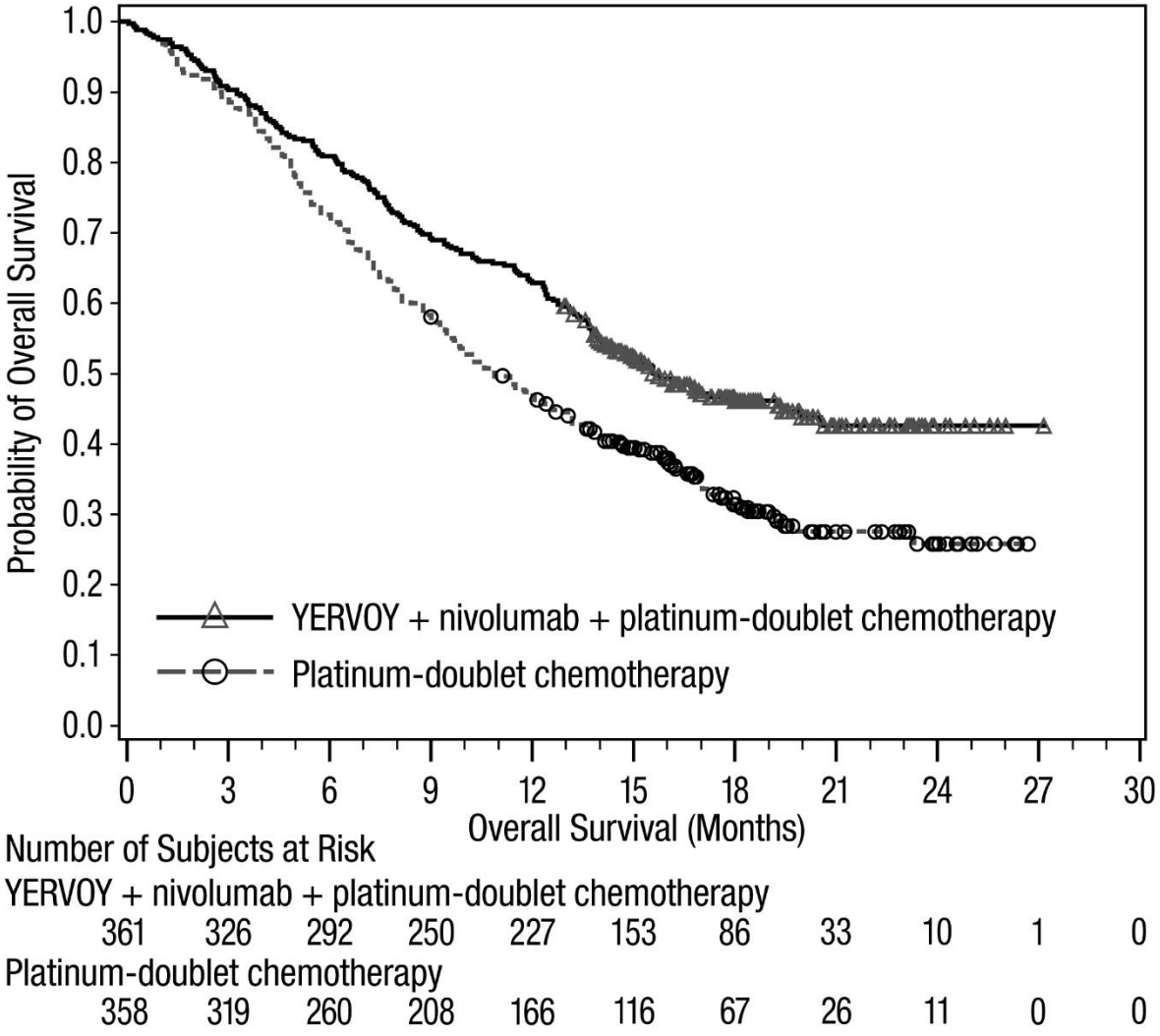
[d] Kaplan-Meier estimate.

[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 YERVOY and nivolumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 9).

Figure 9: Overall Survival - CHECKMATE-9LA



14.7 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:

- YERVOY 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks and nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 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 YERVOY were permitted to continue nivolumab 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 YERVOY in combination with nivolumab (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 YERVOY in combination with nivolumab compared to chemotherapy. Efficacy results from the prespecified interim analysis are presented in Table 35 and Figure 10.

Table 35: Efficacy Results - CHECKMATE-743

	YERVOY and Nivolumab (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		
Median (months)[a] (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.

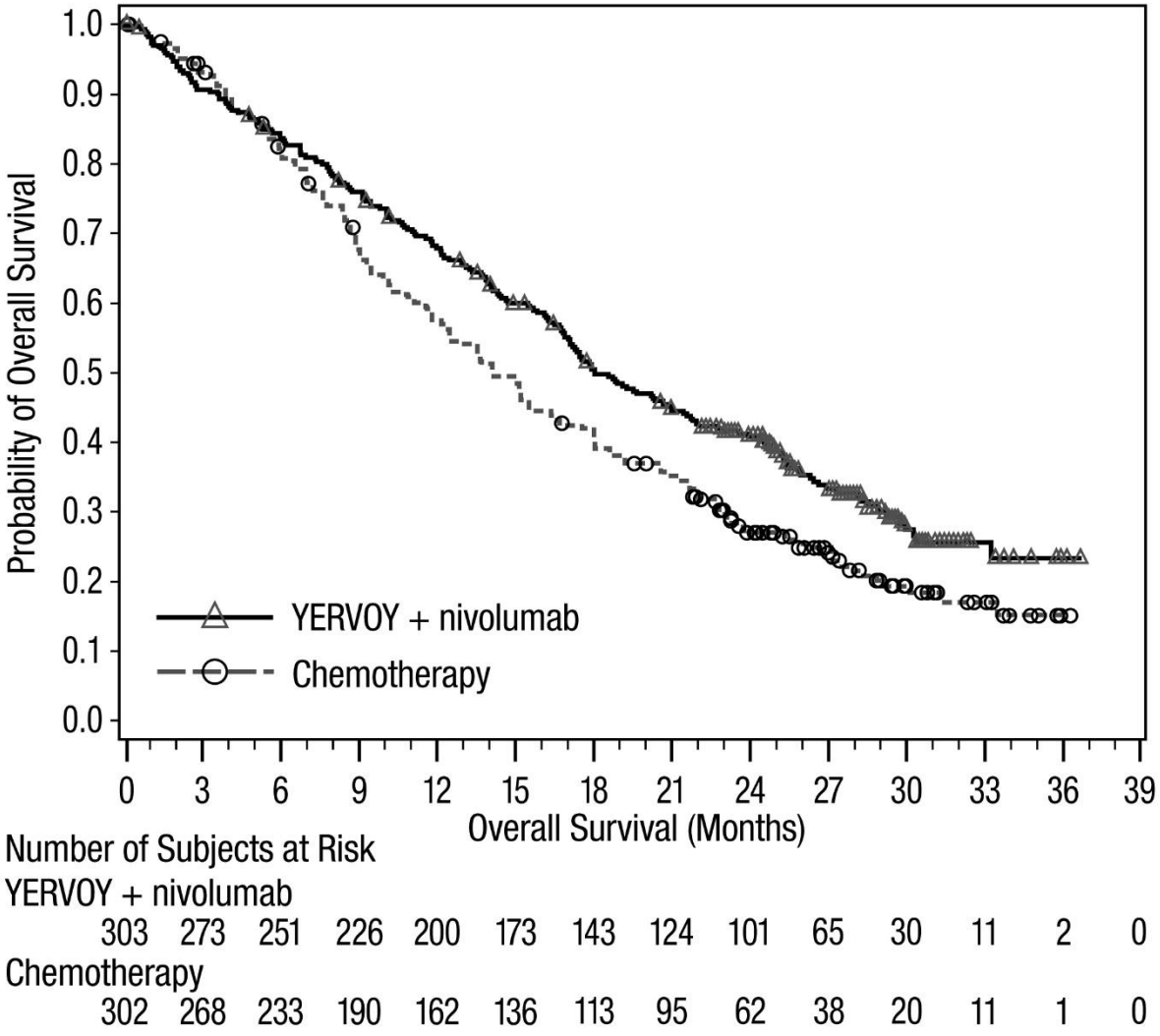
[b] Kaplan-Meier estimate.

[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 10: 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 YERVOY and nivolumab 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 YERVOY and nivolumab arm and 8.8 months in the chemotherapy arm.

14.8 Esophageal Cancer

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. Patients were not

amenable to chemoradiation or surgery with curative intent. 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. 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:

- YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 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 were treated until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab 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 649 patients were randomized in Arms A and C of the CHECKMATE-648 study, among whom 644 and 601 patients had quantifiable TC PD-L1 expression and CPS at baseline, respectively; 84% (546/649) 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 81), 45% were ≥65 years of age, 84% were male, 71% were Asian, 25% were White, and 1.6% were Black or African American. Patients had histological confirmation of squamous cell carcinoma (99%) or adenosquamous cell carcinoma (1.3%) in the esophagus. Baseline ECOG performance status was 0 (46%) or 1 (54%).

A statistically significant improvement in OS was demonstrated in patients randomized to YERVOY in combination with nivolumab compared with chemotherapy; however, an exploratory analysis of OS in patients with PD-L1 CPS <1 showed a HR of 1.0 (95% CI 0.52, 1.94), including 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 36 and Figures 11 and 12.

Table 36: Efficacy Results - Arms A and C of CHECKMATE-648

	YERVOY and Nivolumab (n=158)	Cisplatin and Fluorouracil (n=157)	YERVOY and Nivolumab (n=266)	Cisplatin and Fluorouracil (n=280)
	TC PD-L1 expression ≥1%		PD-L1 CPS ≥1	
Overall Survival				
Deaths (%)	106 (67)	121 (77)	179 (67)	205 (73)
Median (months) (95% CI)	13.7 (11.2, 17.0)	9.1 (7.7, 10)	12.7 (10.9, 15.5)	9.8 (8.8, 11.6)
Hazard ratio (95% CI)[b]	0.64 (0.49, 0.84)		0.76 (0.62, 0.93)	
p-value[c]	0.0010[S1]		-	
Progression-free Survival[a]				
Disease progression or death (%)	123 (78)	100 (64)	206 (77)	184 (66)
Median (months) (95% CI)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)	2.8 (2.6, 4.2)	5.6 (4.2, 5.9)
Hazard ratio (95% CI)[b]	1.02 (0.78, 1.34)		1.2 (1.0, 1.5)	
p-value[c]	NS		-	
Overall Response Rate, n (%)[a], NT	56 (35.4)	31 (19.7)	74 (28)	76 (27)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)	(22.5, 33.6)	(22.0, 32.8)
Complete response (%)	28 (17.7)	8 (5.1)	32 (12.0)	18 (6.4)
Partial response (%)	28 (17.7)	23 (14.6)	42 (15.8)	58 (20.7)
Median (95% CI)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)	11.8 (7.1, 23.6)	6.9 (5.7, 8.2)
Range	1.4+, 34.5+	1.4+, 31.8+	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 nivolumab- containing arm compared to chemotherapy within each analysis population.

[c] Based on a stratified 2-sided log-rank test.

[S1] Significant p-value compared to stopping boundary of 0.014.

NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure.

Figure 11: Overall Survival - CHECKMATE-648

(A) OS in TC PD-L1 ≥1% (B) OS in PD-L1 CPS ≥1

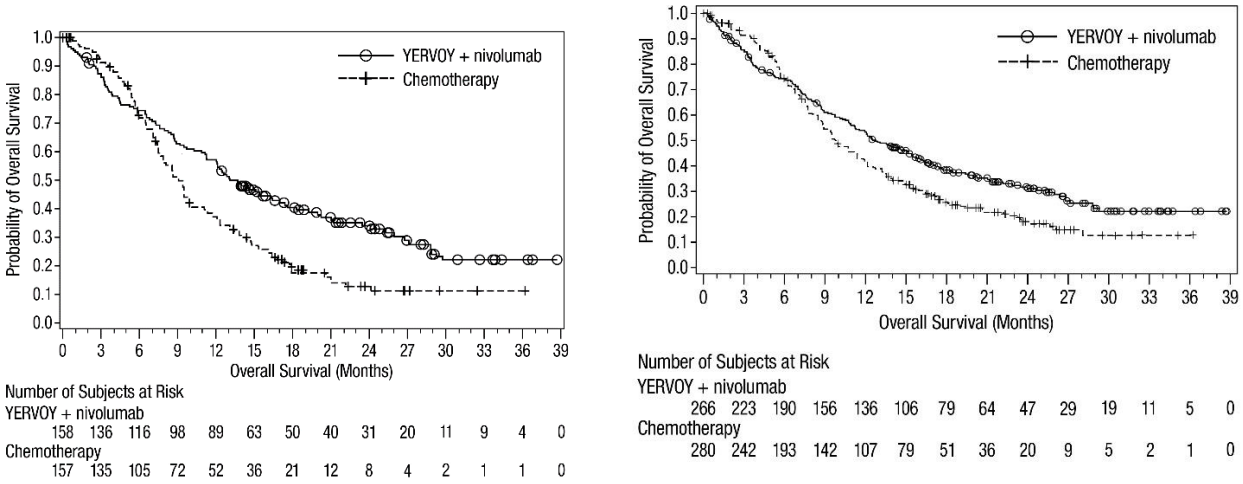
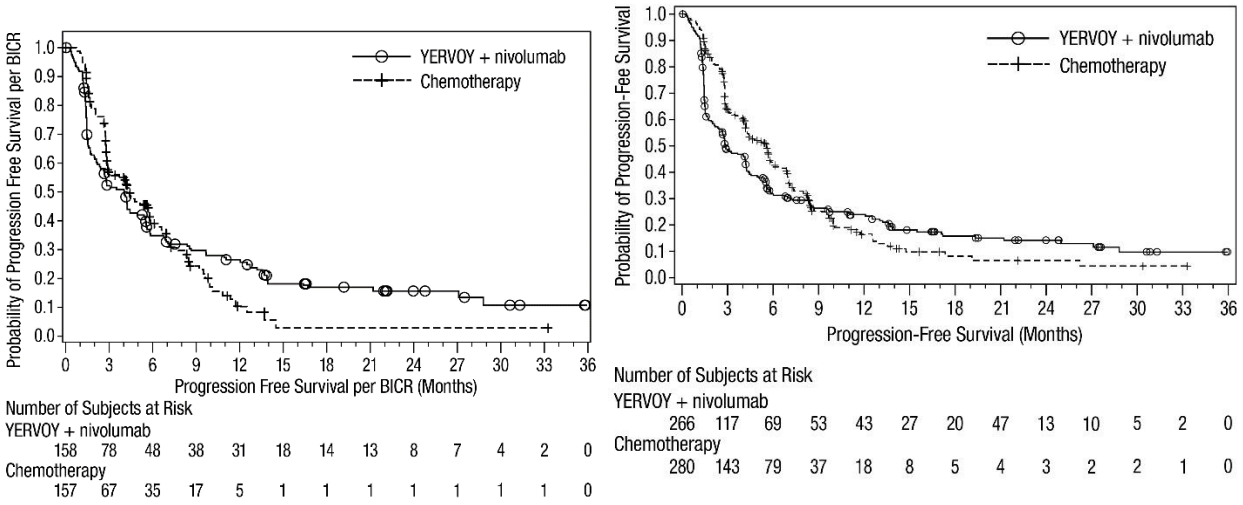


Figure 12: Progression-free Survival – CHECKMATE-648

(A) PFS in TC PD-L1 ≥1% (B) PFS in PD-L1 CPS ≥1



16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY (ipilimumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution. YERVOY is available as follows:

Carton Contents	NDC
One 50 mg/10 mL (5 mg/mL), single-dose vial	NDC 0003-2327-11
One 200 mg/40 mL (5 mg/mL), single-dose vial	NDC 0003-2328-22

Store YERVOY under refrigeration at 2°C to 8°C (36°F to 46°F). Protect YERVOY from light by storing in the original carton 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

Advise patients that YERVOY can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.
- Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus.
- Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.
- Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

- Advise patients who are receiving YERVOY of the potential risk of an infusion-related reaction *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise patients who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-844-593-7869 *[see Use in Specific Populations (8.1)]*.

Lactation

- Advise women not to breastfeed during treatment with YERVOY and for 3 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

[print code]

MEDICATION GUIDE
YERVOY® (yur-voi)
(ipilimumab)
injection

Read this Medication Guide before you start receiving YERVOY and before each infusion. There may be new information. If your healthcare provider prescribes YERVOY in combination with nivolumab, also read the Medication Guide that comes with nivolumab. 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 YERVOY?

YERVOY is a medicine that may treat certain cancers by working with your immune system. YERVOY 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. You may have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when YERVOY is used in combination with nivolumab.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

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

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores in mouth or nose, throat, or genital area

Hormone gland problems.

- headache 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

Lung problems.

- new or worsening cough
- shortness of breath
- chest pain

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Eye problems.

- blurry vision, double vision, or other vision problems
- eye pain or redness

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 YERVOY. Call or see your healthcare provider right away for any new or worsening signs or symptoms.

- 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

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with YERVOY. 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 YERVOY if you have severe side effects.

What is YERVOY?

YERVOY is a prescription medicine used:

- **to treat a kind of skin cancer called melanoma.**

- YERVOY may be used alone or in combination with nivolumab in adults and children 12 years of age and older when melanoma has spread or cannot be removed by surgery.
- YERVOY may be used alone in adults to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.

- **in adults with kidney cancer (renal cell carcinoma).** YERVOY may be used in combination with nivolumab in certain people when their cancer has spread.
- **in adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).**
  - YERVOY may be used in combination with nivolumab 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).
- **in adults with liver cancer (hepatocellular carcinoma).**
  - YERVOY may be used in combination with nivolumab as your first treatment when your liver cancer:
    - cannot be removed by surgery, **or**
    - has spread.
  - YERVOY may be used in combination with nivolumab when your liver cancer:
    - cannot be removed by surgery, **or**
    - has spread, **and**
    - you have received prior treatment with sorafenib.
- **in adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - YERVOY may be used in combination with nivolumab 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.
  - YERVOY may be used in combination with nivolumab 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 grown, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.
- **in adults with a type of cancer that affects the lining of the lungs and chest wall called malignant pleural mesothelioma.**
  - YERVOY may be used in combination with nivolumab as your first treatment for malignant pleural mesothelioma that cannot be removed by surgery.
- **in adults with cancer of the tube that connects your throat to your stomach (esophageal cancer).**
  - YERVOY may be used in combination with nivolumab as your first treatment when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery (advanced), or has spread to the other parts of the body (metastatic), **and**
    - your tumors are positive for PD-L1.

It is not known if YERVOY is safe and effective in children younger than 12 years of age with melanoma that has spread or cannot be removed by surgery, or with MSI-H or dMMR metastatic colorectal cancer.
It is not known if YERVOY is safe and effective in children for the treatment of any other cancers.

Before you receive YERVOY, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems such as ulcerative colitis, Crohn's disease, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. YERVOY can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will give you a pregnancy test before you start treatment with YERVOY.
  - You should use an effective method of birth control during treatment and for 3 months after your last dose of YERVOY. 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 or think you may be pregnant during treatment with YERVOY. You or your healthcare provider should contact Bristol-Myers Squibb at 1-844-593-7869 as soon as you become aware of a pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if YERVOY passes into your breast milk. Do not breastfeed during treatment and for 3 months after your last dose of YERVOY.

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 YERVOY?

- Your healthcare provider will give you YERVOY into your vein through an intravenous (IV) line.
- YERVOY is usually given over **30** minutes.
- If you are receiving YERVOY as treatment for melanoma that has been removed by surgery to help prevent it from coming back, YERVOY will be given over **30** minutes.

- In combination with nivolumab, YERVOY is usually given every 3 weeks for up to 4 doses. After that, nivolumab alone is usually given every 2 or 4 weeks.
- For NSCLC that has spread to other parts of your body, YERVOY is given every 6 weeks and nivolumab is given every 3 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 that cannot be removed by surgery, YERVOY is given every 6 weeks and nivolumab is given every 3 weeks for up to 2 years.
- When YERVOY is used in combination with nivolumab for esophageal squamous cell carcinoma (ESCC), YERVOY is given every 6 weeks and nivolumab is given every 2 or 3 weeks for up to 2 years.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests before starting and during treatment with YERVOY.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of YERVOY?

YERVOY can cause serious side effects, including:

- **See** "**What is the most important information I should know about YERVOY?**"
- **Severe infusion-related reactions.** Tell your healthcare provider or nurse right away if you get these symptoms during an infusion of YERVOY:
  - chills or shaking
  - itching or rash
  - flushing
  - shortness of breath or wheezing
  - dizziness
  - feel like passing out
  - fever
  - back or neck pain
- **Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with YERVOY. Your healthcare provider will monitor you for these complications.

The most common side effects of YERVOY when used alone include:

- feeling tired
- diarrhea
- nausea
- itching
- rash
- vomiting
- headache
- weight loss
- fever
- decreased appetite
- difficulty falling or staying asleep

The most common side effects of YERVOY when used in combination with nivolumab 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 YERVOY when used in combination with nivolumab and chemotherapy include:

- feeling tired
- pain in muscles, bones, and joints
- nausea
- diarrhea
- rash
- decreased appetite
- constipation
- itching

These are not all of the possible side effects of YERVOY.

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 YERVOY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about YERVOY, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about YERVOY that is written for health professionals.

What are the ingredients of YERVOY?

Active ingredient: ipilimumab

Inactive ingredients: diethylene triamine pentaacetic acid (DTPA), mannitol, polysorbate 80 (vegetable origin), sodium chloride, tris hydrochloride, and Water for Injection

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
U.S. License No. 1713

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For more information, call 1-800-321-1335

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2025

米国添付文書の邦訳（概要）

国名	米国
販売名	YERVOY (ipilimumab) injection, for intravenous use
会社名	Bristol-Myers Squibb Company（Princeton、NJ 08543 USA）
一般的名称	イピリムマブ
承認年月日	2011 年 3 月 25 日
剤型・含量	注射剤：50 mg/10 mL（5 mg/mL）及び 200 mg/40 mL（5 mg/mL）
効能・効果	**1.1 切除不能又は転移性悪性黒色腫** YERVOY は、成人及び 12 歳以上の小児における切除不能又は転移性悪性黒色腫に対する単剤又は nivolumab との併用療法を適応とする。 **1.2 悪性黒色腫の術後補助療法** YERVOY は、領域リンパ節への 1 mm を超える病理学的転移を有し、全リンパ節廓清を含む完全切除術を受けた皮膚黒色腫の成人患者の術後補助療法を適応とする。 **1.3 進行腎細胞癌** YERVOY は、intermediate 又は poor リスクの進行腎細胞癌の成人患者に対する一次治療として、nivolumab との併用療法を適応とする。 **1.4 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の転移性結腸・直腸癌** YERVOY 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-High）又はミスマッチ修復機構欠損（dMMR）を有する成人及び 12 歳以上の小児の結腸・直腸癌（CRC）に対する nivolumab との併用を適応とする。 **1.5 肝細胞癌** • YERVOY は、切除不能又は転移性肝細胞癌（HCC）の成人患者に対する一次療法として、nivolumab との併用療法を適応とする。 • YERVOY は、ソラフェニブ治療歴のある切除不能又は転移性 HCC の成人患者に対する nivolumab との併用を適応とする。 **1.6 転移性非小細胞肺癌** YERVOY は、FDA により承認された検査*［用法・用量（2.1）参照］*で腫瘍に PD-L1 発現（1%以上）が確認され、EGFR 又は ALK 遺伝子変異を有さない転移性の非小細胞肺癌（NSCLC）の成人患者に対する一次治療として、nivolumab との併用を適応とする。 YERVOY は、EGFR 又は ALK 遺伝子変異を有さない転移性又は再発性の NSCLC の成人患者に対する一次治療として、nivolumab 及び 2 サイクルのプラチナ製剤を含む 2 剤併用化学療法との併用を適応とする。 **1.7 悪性胸膜中皮腫** YERVOY は、切除不能な悪性胸膜中皮腫の成人患者に対する一次治療として、nivolumab との併用を適応とする。 **1.8 食道癌** YERVOY は、腫瘍に PD-L1 発現（1%以上）が確認された*［用法・用量（2.1）参照］*、切除不能な進行性又は転移性の食道扁平上皮癌（ESCC）の成人患者に対する一次療法として、nivolumab との併用を適応とする。

用法・用量

2.1 患者の選択

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より入手可能である。

https://www.fda.gov/CompanionDiagnostics

非小細胞肺癌

- YERVOY と nivolumab を併用して転移性 NSCLC 患者を治療する場合は、PD-L1 発現状態に基づいて患者を選択すること。*［臨床試験（14.6）参照］*

食道癌

- YERVOY と nivolumab を併用して切除不能な進行又は転移性の ESCC 患者を治療する場合は、PD-L1 発現状態に基づいて患者を選択すること。*［臨床試験（14.8）参照］*
  - 進行又は転移性 ESCC 患者における PD-L1 発現検出のための FDA 承認済のコンパニオン診断薬はない。

2.2 推奨用量

YERVOY 単剤投与の推奨用量を表 1 に示す。

YERVOY を 30 分間かけて点滴静注する*［調整と投与（2.4）参照］*。

表 1: YERVOY 単剤投与の推奨用量

適応症	推奨される YERVOY 用量	治療期間
切除不能又は転移性悪性黒色腫	3 mg/kg を 3 週間ごと	4 回まで
悪性黒色腫の術後補助療法	3 mg/kg を 3 週間ごと その後 3 mg/kg を 12 週間ごと	3 週間ごと 4 回まで 12 週間ごと最大 4 回追加投与

他の治療薬と併用する場合の YERVOY の推奨用量を表 2 に示す。YERVOY は他の治療薬と同じ日に投与する。

必要に応じて、YERVOY と併用投与する各治療薬の推奨用量情報を参照すること。

表 2: 他の治療薬と併用する場合の YERVOY の推奨用量*

適応症	推奨される YERVOY 用量	治療期間
切除不能又は転移性悪性黒色腫	3 mg/kg を 3 週間ごと nivolumab 1 mg/kg と併用	nivolumab との併用で最大 4 回、 4 回の併用療法終了後、nivolumab の単剤投与を疾患進行又は許容できない毒性が認められるまで†
進行腎細胞癌	1 mg/kg を 3 週間ごと nivolumab 3 mg/kg と併用	nivolumab との併用で最大 4 回、 4 回の併用療法終了後、nivolumab の単剤投与を疾患進行又は許容できない毒性が認められるまで†

	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）の転移性結腸・直腸癌	成人患者及び 12 歳以上で体重 40 kg 以上の小児患者： 1 mg/kg を 3 週間ごと nivolumab 240 mg と併用	nivolumab との併用で最大 4 回† 4 回の併用療法終了後、nivolumab の単剤投与を疾患進行、許容できない毒性が認められるまで又は最長 2 年間†
		12 歳以上かつ体重 40 kg 未満の小児患者： 1 mg/kg を 3 週間ごと nivolumab 3 mg/kg と併用	
	肝細胞癌	3 mg/kg を 3 週間ごと nivolumab 1 mg/kg と併用	nivolumab との併用で最大 4 回、 最大 4 回の併用療法終了後、nivolumab の単剤投与を疾患進行又は許容できない毒性が認められるまで†
	PD-L1 発現転移性非小細胞肺癌	1 mg/kg を 6 週間ごと nivolumab 360 mg を 3 週間ごと併用	nivolumab との併用で、疾患進行、許容できない毒性が認められるまで、又は疾患進行が認められない患者では最長 2 年間†
	転移性又は再発の非小細胞肺癌	1 mg/kg を 6 週間ごと nivolumab 360 mg を 3 週間ごと併用 及び組織型に応じたプラチナ製剤を含む 2 剤併用化学療法を 3 週間ごと	nivolumab との併用で、疾患進行、許容できない毒性が認められるまで、又は疾患進行が認められない患者では最長 2 年間†
			組織型に応じたプラチナ製剤を含む 2 剤併用化学療法を 2 サイクル投与
	悪性胸膜中皮腫	1 mg/kg を 6 週間ごと nivolumab 360 mg を 3 週間ごと併用	nivolumab との併用で、疾患進行、許容できない毒性が認められるまで、又は疾患進行が認められない患者では最長 2 年間†
	食道扁平上皮癌	1 mg/kg を 6 週間ごと nivolumab 3 mg/kg を 2 週間ごと又は 360 mg を 3 週間ごと併用	nivolumab との併用で、疾患進行、許容できない毒性が認められるまで、又は最長 2 年間

* YERVOY と併用する薬剤の推奨用量については、必要に応じて各薬剤の添付文書を参照すること。

† YERVOY との併用投与終了後の用法・用量については、nivolumab の添付文書を参照のこと。

2.3 副作用に対する推奨される用量調節

YERVOY の減量は推奨されない。通常、重度（Grade 3）の免疫介在性副作用の場合は YERVOY の投与を中断する。生命を脅かす（Grade 4）免疫介在性副作用、全身免疫抑制療法を必要とする重度（Grade 3）の免疫介在性反応の再発、YERVOY の最終投与後 12 週間以上持続する中等度（Grade 2）又は重度（Grade 3）の持続性反応の場合（内分泌障害を除く）、又はステロイド投与開始後 12 週間以内に副腎皮質ステロイドをプレドニゾロン換算で 10 mg/日以下に減量できない場合は、YERVOY の投与を中止する。これらの一般的なガイドラインとは異なる管理が必要な副作用に対する YERVOY 又は nivolumab と併用する YERVOY の用量調節を表 3 に要約する。

YERVOY を nivolumab と併用投与している場合、毒性が認められたら YERVOY 及び nivolumab の両剤の投与を中断又は中止する。

表 3：副作用に対する推奨される用量調節

副作用	重症度*	用量調節
免疫介在性副作用 *［警告及び使用上の注意（5.1）参照］*		
大腸炎	Grade 2	投与中断 [a]
	Grade 3 又は 4	投与中止
肝臓に腫瘍が浸潤していない肝炎 又は 肝臓に腫瘍浸潤を伴う肝炎/非 HCC	AST 又は ALT が ULN の 3 倍超～5 倍以下に増加 又は 総ビリルビンが ULN の 1.5 倍超～3 倍以下に増加	投与中断 [a]
	AST 又は ALT が ULN の 5 倍超 又は 総ビリルビンが ULN の 3 倍超	投与中止
肝臓に腫瘍浸潤を伴う肝炎 [b]/HCC[c]	ベースラインの AST/ALT が ULN の 1 倍超～3 倍以下かつ 5 倍超～10 倍以下の増加 又は ベースラインの AST/ALT が ULN の 3 倍超～5 倍以下かつ 8 倍超～10 倍以下の増加	投与中断 [a]
	AST/ALT が ULN の 10 倍超に増加 又は 総ビリルビンが ULN の 3 倍超に増加	投与中止
剥脱性皮膚疾患	SJS、TEN、又は DRESS の疑い	投与中断
	SJS、TEN、又は DRESS の確定	投与中止

	内分泌障害 [d]	Grade 3 又は 4	臨床的に安定するまで投与中断又は重症度に応じて投与中止
	肺臓炎	Grade 2	投与中断 [a]
		Grade 3 又は 4	投与中止
	腎機能障害を伴う腎炎	Grade 2 又は 3 の血中クレアチニン増加	投与中断 [a]
		Grade 4 の血中クレアチニン増加	投与中止
	神経毒性 [c]	Grade 2	投与中断 [a]
		Grade 3 又は 4	投与中止
	心筋炎	Grade 2、3、又は 4	投与中止
	眼科疾患	局所療法を受けているが 2 週間以内に Grade 1 に改善しない、又は全身療法を必要とする Grade 2、3、又は 4	投与中止
	その他の副作用		
	注入に伴う反応 *［警告及び使用上の注意（5.2）参照］*	Grade 1 又は 2	投与中断又は注入速度を減速する
		Grade 3 又は 4	投与中止
	ALT＝アラニンアミノトランスフェラーゼ、AST＝アスパラギン酸アミノトランスフェラーゼ、DRESS＝好酸球増加と全身症状を伴う薬物反応、SJS＝スティーブンス・ジョンソン症候群、TEN＝中毒性表皮壊死融解症、ULN＝基準値上限 [*] Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 に基づく。 [a] 副腎皮質ステロイドを漸減して完全又は部分的に回復（Grade0 又は 1）した患者で再開する。最終投与から 12 週間以内に完全又は部分的な回復が認められない場合、又はステロイド開始から 12 週間以内にプレドニゾンを 10 mg/日（又は同等品）以下に減量できない場合は、投与を中止する。 [b] ベースラインの AST/ALT が ULN 以下であった場合は、肝障害を伴わない肝炎の推奨用量に基づき、YERVOY を投与中断又は投与中止する。 [c] このガイダンスは、nivolumab と併用で YERVOY の投与を受けている HCC 患者にのみ適用される。 [d] 臨床的重症度に応じて、ホルモン補充療法により症状が改善するまで、Grade 2 の内分泌障害が発現した場合は投与中断を考慮する。急性症状が回復したら再開する。		
禁忌	なし		
警告及び使用上の注意	**5.1 重度及び致死性の免疫介在性副作用** YERVOY は完全ヒトモノクローナル抗体であり、CTLA-4 経路により誘発される T 細胞抑制シグナルを遮断することにより、免疫介在性副作用を誘発する可能性のある免疫反応の抑制を解除する。本項に記載されている免疫介在性副作用には、起こりうるすべての重度及び致死性の免疫介在性反応が含まれているわけではない。		

	免疫介在性副作用は、重度又は死に至る場合があり、あらゆる器官系又は組織に発現する可能性がある。免疫介在性副作用は、YERVOY の投与開始後いつでも発現する可能性がある。免疫介在性副作用は通常投与中に発現するが、YERVOY の投与中止後にも発現することがある。 YERVOY を確実に安全に投与するには、早期の特定と管理が不可欠である。潜在的な免疫介在性副作用の臨床症状と考えられる徴候及び症状をモニタリングする。ベースライン時及び各投与前に、肝酵素、クレアチニン、副腎皮質刺激ホルモン（ACTH）濃度及び甲状腺機能を含む臨床生化学検査値を評価する。必要に応じて専門医による診察を含む医学的管理を速やかに実施する。 重症度に応じて YERVOY の投与を中断又は中止すること。*［用法・用量（2.3）参照］* 通常、YERVOY の投与中断又は中止が必要な場合は、Grade1 以下に改善するまで全身副腎皮質ステロイド療法（プレドニゾン換算で 1～2 mg/kg/日）を実施する。Grade1 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 ヵ月以上かけて漸減する。副腎皮質ステロイドで免疫介在性副作用がコントロールできない患者には、他の免疫抑制剤の全身投与を考慮すること。 <u>免疫介在性の大腸炎</u> YERVOY は免疫介在性の大腸炎を引き起こす可能性があり、死に至ることもある。サイトメガロウイルス（CMV）感染/再活性化はコルチコステロイド不応性免疫介在性の大腸炎の患者で報告されている。コルチコステロイド不応性の大腸炎の場合は、感染症の精密検査を繰り返して、別の病因を除外することを検討すべきである。 *YERVOY 3 mg/kg 単剤投与* YERVOY 3 mg/kg の単剤投与を受けた患者の 12%（62/511 例）に免疫介在性の大腸炎が認められ、内訳は Grade 3～5 が 7%、Grade 2 が 5%であった。大腸炎により、患者の 4.3%で YERVOY の投与を中止し、0.2%で YERVOY の投与を少なくとも 1 回中断した。 免疫介在性の大腸炎患者の 74%（46/62 例）で、副腎皮質ステロイドの全身投与を要した。5 例では別の免疫抑制剤と副腎皮質ステロイドの併用投与を必要とした。大腸炎は 62 例中 76%で回復した。1 例は大腸炎のため YERVOY の投与を 1 回以上中断し、症状改善後に追加投与を受けた患者はいなかった。 *YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 9%（60/666 例）に免疫介在性の大腸炎が認められ、内訳は Grade 3 が 4.4%、Grade 2 が 3.7%であった。大腸炎により、患者の 3.2%で YERVOY と nivolumab の投与を中止し、2.7%で YERVOY と nivolumab の投与を中断した。 YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者では、副腎皮質ステロイドの全身投与が免疫介在性の大腸炎の特定に必要な診断基準の 1 つであった。したがって、免疫介在性の大腸炎患者の 100%（60/60 例）で、副腎皮質ステロイドの全身投与を要した。約 23%では別の免疫抑制剤と副腎皮質ステロイドの併用投与を必要とした。大腸炎は 60 例中 95%で回復した。大腸炎のため YERVOY 又は nivolumab の投与を中断した患者 18 例のうち、16 例が症状改善後に追加投与を受けた。このうち 10 例で大腸炎が再発した。 *YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 25%（115/456 例）に免疫介在性の大腸炎が認められ、

	内訳は Grade 4 が 0.4%、Grade 3 が 14%、Grade 2 が 8%であった。大腸炎により、YERVOY と nivolumab の投与を患者の 14%で中止し、4.4%で中断した。 大腸炎患者の 100%（115/115 例）で、副腎皮質ステロイドの全身投与を要した。患者の約 23%がインフリキシマブの追加と高用量コルチコステロイドを必要とした。大腸炎は 115 例中 93%で回復した。大腸炎のため YERVOY と nivolumab の投与を中断した 20 例の患者のうち、16 例が症状改善後に治療を再開し、このうち 9 例で大腸炎が再発した。 免疫性肝炎 *YERVOY 3 mg/kg 単剤投与* YERVOY 3 mg/kg の単剤投与を受けた患者の 4.1%（21/511 例）に免疫介在性の肝炎が認められ、内訳は Grade 3～5 が 1.6%、Grade 2 が 2.5%であった。肝炎により、患者の 0.4%で YERVOY の投与を中止し、YERVOY の投与を少なくとも 1 回中断した患者はいなかった。 免疫介在性の肝炎患者の 29%（6/21 例）で、副腎皮質ステロイドの全身投与を要した。別の免疫抑制剤と副腎皮質ステロイドの併用投与を必要とした患者はいなかった。肝炎は 21 例中 86%で回復した。 *YERVOY 3 mg/kg とベムラフェニブの併用* ベムラフェニブと併用した YERVOY の安全性及び有効性は確立されていない。*［効能・効果（1）参照］*用量設定試験で、YERVOY（3 mg/kg）及びベムラフェニブ（960 mg 回又は 720 mg を 1 日 2 回）を併用投与された患者 10 例中 6 例で、総ビリルビン増加を伴う、あるいは伴わない Grade 3 のトランスアミナーゼ増加が認められた。 *YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 7%（48/666 例）に免疫介在性の肝炎が認められ、内訳は Grade 4 が 1.2%、Grade 3 が 4.9%、Grade 2 が 0.4%であった。肝炎により、患者の 3.6%で YERVOY と nivolumab の投与を中止し、2.6%で YERVOY と nivolumab の投与を中断した。 YERVOY1 mg/kg と nivolumab の併用投与を受けた患者では、副腎皮質ステロイドの全身投与が免疫介在性の肝炎の特定に必要な診断基準の 1 つであった。したがって、免疫介在性の肝炎患者の 100%（48/48 例）で、副腎皮質ステロイドの全身投与を要した。約 19%では別の免疫抑制剤と副腎皮質ステロイドの併用投与を必要とした。肝炎は 48 例中 88%で回復した。肝炎のため YERVOY 又は nivolumab の投与を中断した患者 17 例のうち、14 例が症状改善後に追加投与を受けた。このうち 10 例で肝炎が再発した。 *YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 15%（70/456 例）に免疫介在性の肝炎が認められ、内訳は Grade 4 が 2.4%、Grade 3 が 11%、Grade 2 が 1.8%であった。免疫介在性の肝炎により、YERVOY と nivolumab の投与を患者の 8%で中止し、3.5%で中断した。 全身性コルチコステロイドは肝炎患者の 100%（70/70 例）で必要であった。免疫介在性肝炎患者の約 9%はミコフェノール酸の追加と高用量コルチコステロイドを必要とした。肝炎は 70 例中 91%で回復した。YERVOY と nivolumab の投与を中断した 16 例の患者のうち、14 例が症状改善後に治療を再開し、このうち 8 例で肝炎が再発した。

	皮膚の免疫介在性副作用 YERVOY は、水疱性及び剥脱性皮膚炎、スティーブンス・ジョンソン症候群及び中毒性表皮壊死融解症（TEN）及び DRESS（好酸球増加と全身症状を伴う薬物反応）など、免疫介在性の発疹又は皮膚炎を引き起こす可能性がある。局所皮膚軟化剤及び／又は局所副腎皮質ステロイドは、軽度から中等度の非水疱性／剥脱性発疹の治療に適切な場合がある。重症度に応じて YERVOY の投与を中断又は中止すること*［用法・用量（2.3）参照］*。 *YERVOY 3 mg/kg 単剤投与* YERVOY 3 mg/kg の単剤投与を受けた患者の 15%（76/511 例）に免疫介在性の発疹が認められ、内訳は Grade 3～5 が 2.5%、Grade 2 が 12%であった。 発疹により、患者の 0.2%で YERVOY の投与を中止し、1.4%で YERVOY の投与を少なくとも 1 回中断した。 免疫介在性の発疹患者の 43%（33/76 例）で、副腎皮質ステロイドの全身投与を要した。発疹は 76 例中 71%で回復した。発疹のため YERVOY の投与を中断した患者 7 例のうち、3 例が症状改善後に追加投与を受けた。このうち 1 例で発疹が再発した。 *YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 16%（108/666 例）に免疫介在性の発疹が認められ、内訳は Grade 3 が 3.5%、Grade 2 が 4.2%であった。発疹により、患者の 0.5%で YERVOY と nivolumab の投与を中止し、2.0%で YERVOY と nivolumab の投与を中断した。 YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者では、副腎皮質ステロイドの全身投与が免疫介在性の発疹の特定に必要な診断基準の 1 つであった。したがって、免疫介在性の発疹患者の 100%（108/108 例）で、副腎皮質ステロイドの全身投与を要した。発疹は 108 例中 75%で回復した。発疹のため YERVOY 又は nivolumab の投与を中断した患者 13 例のうち、11 例が症状改善後に追加投与を受けた。このうち 5 例で発疹が再発した。 *YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 28%（127/456 例）に免疫介在性の発疹が認められ、内訳は Grade 3 が 4.8%、Grade 2 が 10%であった。免疫介在性発疹により、YERVOY と nivolumab の投与を患者の 0.4%で中止し、3.9%で中断した。 全身性コルチコステロイドは免疫介在性発疹患者の 100%（127/127 例）で必要であった。発疹は 127 例中 84%で回復した。発疹により YERVOY と nivolumab の投与を中断した 18 例の患者のうち、15 例が症状改善後に治療を再開し、このうち 8 例で発疹が再発した。 免疫性内分泌障害 *YERVOY 3 mg/kg 単剤投与* YERVOY 3 mg/kg の単剤投与を受けた患者の 4%（21/511 例）に Grade 2～5 の免疫介在性の内分泌障害が認められた。 重度から生命を脅かす（Grade 3～4）内分泌障害が 9 例（1.8%）に発現した。これらの 9 例はいずれも下垂体機能低下症を有しており、副腎機能不全、性腺機能低下症及び甲状腺機能低下症などの内分泌障害を併発している患者もいた。9 例中 6 例は重度の内分泌障害のため入院した。 甲状腺機能低下症、副腎機能不全、下垂体機能低下症、甲状腺機能亢進症、クッシング症候群など、中等度（Grade 2）の内分泌障害が 12 例（2.3%）に発現した。

	中等度～生命を脅かす内分泌障害を発現した患者 21 例のうち、17 例が長期のホルモン補充療法を要し、内訳として副腎皮質ホルモン（10 例）及び甲状腺ホルモン（13 例）が多かった。 *YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用* *下垂体炎：* YERVOY 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すことがある。臨床的に必要であれば、ホルモン補充療法を開始する。重症度に応じて YERVOY の投与を中断又は中止すること*［用法・用量（2.3）参照］*。 RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 4.4%（29/666 例）に下垂体炎が認められ、内訳は Grade 4 が 0.3%、Grade 3 が 2.4%、Grade 2 が 0.9%であった。下垂体炎により、患者の 1.2%で YERVOY と nivolumab の投与を中止し、2.1%で YERVOY と nivolumab の投与を中断した。下垂体炎患者の約 72%がホルモン補充療法を受けた。免疫介在性の下垂体炎患者の 72%（21/29 例）で、副腎皮質ステロイドの全身投与を要した。下垂体炎は 29 例中 59%で回復した。下垂体炎のため YERVOY 又は nivolumab の投与を中断した患者 14 例のうち、11 例が症状改善後に追加投与を受けた。このうち 2 例で下垂体炎が再発した。 *副腎機能不全：* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 7%（48/666 例）に副腎機能不全が認められ、内訳は Grade 4 が 0.3%、Grade 3 が 2.5%、Grade 2 が 4.1%であった。副腎機能不全により、患者の 1.2%で YERVOY と nivolumab の投与を中止し、2.1%で YERVOY と nivolumab の投与を中断した。副腎機能不全患者の約 94%がホルモン補充療法を受けた。副腎機能不全患者の 94%（45/48 例）で、副腎皮質ステロイドの全身投与を要した。副腎機能不全は 48 例中 29%で回復した。副腎機能不全のため YERVOY 又は nivolumab の投与を中断した患者 14 例のうち、11 例が症状改善後に追加投与を受けた。このうち 2 例で副腎機能不全が再発した。 *甲状腺機能亢進症：* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 12%（80/666 例）に甲状腺機能亢進症が認められ、内訳は Grade 3 が 0.6%、Grade 2 が 4.5%であった。甲状腺機能亢進症により YERVOY の投与を中止した患者はいなかった。甲状腺機能亢進症により、患者の 2.3%で YERVOY と nivolumab の投与を中断した。約 19%が甲状腺合成阻害剤の投与を受けた。甲状腺機能亢進症患者の 20%（16/80 例）で、副腎皮質ステロイドの全身投与を要した。甲状腺機能亢進症は 80 例中 85%で回復した。甲状腺機能亢進症のため YERVOY 又は nivolumab の投与を中断した患者 15 例のうち、11 例が症状改善後に追加投与を受けた。このうち 3 例で甲状腺機能亢進症が再発した。 *甲状腺機能低下症：* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 18%（122/666 例）に甲状腺機能低下症が認められ、内訳は Grade 3 が 0.6%、Grade 2 が 11%であった。甲状腺機能低下症により、患者の 0.2%で YERVOY と nivolumab の投与を中止し、1.4%で YERVOY と nivolumab の投与を中断した。約 82%が甲状腺ホルモン補充療法を受けた。甲状腺機能低下症患者の 7%（9/122 例）で、副腎皮質ステロイドの全身投与を要した。甲状腺機能低下症は 122 例中 27%で回復した。甲状腺機能低下症のため YERVOY 又は nivolumab の投与を中断した患者

	9 例のうち、5 例が症状改善後に追加投与を受けた。このうち 1 例で甲状腺機能低下症が再発した。 *甲状腺炎：* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 2.7%（22/666 例）に甲状腺炎が認められ、内訳は Grade 3 が 4.5%、Grade 2 が 2.2%であった。甲状腺炎により、患者の 0.2%で YERVOY と nivolumab の投与を中止し、0.8%で YERVOY と nivolumab の投与を中断した。甲状腺炎患者の 18%（4/22 例）で、副腎皮質ステロイドの全身投与を要した。甲状腺炎は 22 例中 64%で回復した。甲状腺炎のため YERVOY 又は nivolumab の投与を中断した患者 5 例のうち、5 例が症状改善後に追加投与を受けた。このうち甲状腺炎が再発した患者はいなかった。 *1 型糖尿病：* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 2.7%（15/666 例）に糖尿病が認められ、内訳は Grade4 が 0.6%、Grade 3 が 0.3%、Grade 2 が 0.9%であった。糖尿病により、患者の 0.5%で YERVOY と nivolumab の投与を中止し、0.5%で YERVOY と nivolumab の投与を中断した。糖尿病患者の 7%（1/15 例）で、副腎皮質ステロイドの全身投与を要した。糖尿病は 15 例中 27%で回復した。糖尿病のため YERVOY 又は nivolumab の投与を中断した患者 3 例のうち、2 例が症状改善後に追加投与を受けた。このうち糖尿病が再発した患者はいなかった。 *YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用* *下垂体炎：* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 9%（42/456 例）に下垂体炎が認められ、内訳は Grade 3 が 2.4%、Grade 2 が 6%であった。下垂体炎により、YERVOY と nivolumab の投与を患者の 0.9%で中止し、4.2%で中断した。 下垂体炎患者の約 86%がホルモン補充療法を受けた。全身性コルチコ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 例中 38%で回復した。下垂体炎により YERVOY と nivolumab の投与を中断した 19 例の患者のうち、9 例が症状改善後に治療を再開し、このうち 1 例で下垂体炎が再発した。 *副腎機能不全：* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 8%（35/456 例）に副腎機能不全が認められ、内訳は Grade 4 が 0.2%、Grade 3 が 2.4%、Grade 2 が 4.2%であった。副腎機能増不全により、YERVOY と nivolumab の投与を患者の 0.4%で中止し、2.0%で中断した。 副腎機能不全患者の約 71%（25/35 例）が全身性コルチコステロイドを含むホルモン補充療法を受けた。副腎機能不全は 35 例中 37%で回復した。副腎機能不全により YERVOY と nivolumab の投与を中断した 9 例の患者のうち、7 例が症状改善後に治療を再開し、進行中の副腎機能不全に対してホルモン補充療法を必要とした *甲状腺機能低下症：* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 併用投与を受けた患者の 20%（91/456 例）に甲状腺機能低下症が認められ、内訳は Grade 3 が 0.4%、Grade 2 が 11%であった。甲状腺機能低下症により、YERVOY と nivolumab の投与を患者の 0.9%で中止し、0.9%で中断した。 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。全身性コルチコ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 例中 41%で回復した。甲状腺機能低下症により YERVOY と nivolumab の投与を中断した 4 例の患者のうち、2 例が症状改善後に治療を再開し、甲状腺機能低下症の再発は認められなかった。 *甲状腺機能亢進症：* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 9%（42/456 例）に甲状腺機能亢進症が認められ、内訳は Grade 3 が 0.9%、Grade 2 が 4.2%であった。甲状腺機能亢進症により、YERVOY と nivolumab の投与を中止した患者はなく、患者の 2.4%で中断した。 甲状腺機能亢進症患者の 26%がメチマゾール、21%がカルビマゾールの投与を受けた。全身性コルチコステロイドは甲状腺機能亢進症患者の 17%（7/42 例）で必要であった。甲状腺機能亢進症は 42 例中 91%で回復した。甲状腺機能亢進症により YERVOY と nivolumab の投与を中断した 11 例の患者のうち、8 例が症状改善後に治療を再開し、このうち 1 例で甲状腺機能亢進症が再発した。 <u>免疫介在性肺臓炎</u> *YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用* RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 3.9%（26/666 例）に免疫介在性の肺臓炎が認められ、内訳は Grade 3 が 1.4%、Grade 2 が 2.6%であった。肺臓炎により、患者の 1.8%で YERVOY と nivolumab の投与を中止し、1.5%で YERVOY と nivolumab の投与を中断した。 YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者では、副腎皮質ステロイドの全身投与が免疫介在性肺臓炎の特定に必要な診断基準の 1 つであった。したがって、免疫介在性の肺臓炎患者の 100%（26/26 例）で、副腎皮質ステロイドの全身投与を要した。約 8%では別の免疫抑制剤と副腎皮質ステロイドの併用投与を必要とした。肺臓炎は 26 例中 92%で回復した。肺臓炎のため YERVOY 又は nivolumab の投与を中断した患者 10 例のうち、10 例が症状改善後に追加投与を受けた。このうち 4 例で肺臓炎が再発した。 NSCLC では、6 週ごとの YERVOY 1 mg/kg 及び 2 週ごとの nivolumab 3 mg/kg の投与を受けた患者の 9%（50/576 例）で免疫介在性肺臓炎が発現し、内訳は Grade 4（0.5%）、Grade 3（3.5%）及び Grade 2（4.0%）の免疫介在性肺臓炎であった。4 例（0.7%）が肺臓炎により死亡した。持続期間の中央値は 1.5 ヵ月（範囲：5 日～25 ヵ月以上）であった。免疫介在性肺臓炎により YERVOY と nivolumab の併用投与の中止又は中断に至った患者の割合はそれぞれ 5%及び 3.6%であった。 肺臓炎が認められた患者全例で全身性コルチコステロイドが必要となり、その後コルチコステロイドを漸減した。肺臓炎は患者の 72%で消失した。YERVOY と nivolumab の併用投与再開後、患者の約 13%（2/16 例）で肺臓炎が再発した。 *YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用* 悪性黒色腫又は HCC の治療として YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間隔で併用投与を受けた患者の 7%（31/456 例）に免疫介在性肺臓炎が認められ、内訳は Grade 4 が 0.2%、Grade 3 が 2.0%、Grade 2 が 4.4%であった。免疫介在性肺臓炎により、YERVOY と nivolumab の投与を患者の 2.9%で中止し、3.9%で中断した。 全身性コルチコステロイドは肺臓炎患者の 100%で必要であった。肺臓炎は 94%で回復した。肺臓炎により YERVOY と nivolumab の投与を中断した 13 例の患者のうち、13 例が症状改善後に治療を再開し、このうち 4 例で肺臓炎が再発した。 <u>腎機能障害を伴う免疫介在性腎炎</u> *YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用*

RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 4.1%（27/666 例）に腎機能障害を伴う免疫介在性の腎炎が認められ、内訳は Grade 4 が 0.6%、Grade 3 が 1.1%、Grade 2 が 2.2%であった。腎機能障害を伴う腎炎により、患者の 1.2%で YERVOY と nivolumab の投与を中止し、1.8%で YERVOY と nivolumab の投与を中断した。

YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者では、副腎皮質ステロイドの全身投与が腎機能障害を伴う免疫介在性の腎炎の特定に必要な診断基準の 1 つであった。したがって、腎機能障害を伴う免疫介在性の腎炎患者の 100%（27/27 例）で、副腎皮質ステロイドの全身投与を要した。腎機能障害を伴う腎炎は 27 例中 67%で回復した。腎炎のため YERVOY 又は nivolumab の投与を中断した患者 12 例のうち、10 例が症状改善後に追加投与を受けた。このうち 4 例で腎炎が再発した。

その他の免疫性副作用

YERVOY を単剤投与又は nivolumab と併用投与する臨床試験全体で、以下に示すとおり、特に明記しない限り、以下の臨床的に重大な免疫介在性副作用が患者の 1%未満に発現し、一部は死亡に至った。

*神経系：*自己免疫性ニューロパチー（2%）、髄膜炎、脳炎、脊髄炎及び脱髄、筋無力症候群／重症筋無力症、ギラン・バレー症候群、神経不全麻痺、運動機能障害

*心血管系：*血管障害、心筋炎、心膜炎、側頭動脈炎、血管炎

*眼：*眼瞼炎、上強膜炎、虹彩炎、眼窩筋炎、強膜炎、ぶどう膜炎。網膜剥離を伴う場合もある。免疫介在性副作用とともにブドウ膜炎を発現した場合は,YERVOY を投与した患者に認められるフォークト・小柳・原田症候群について検討すること。永久的な視力喪失のリスクを低減するため、全身性コルチコステロイド投与による治療が必要となる場合がある。

*消化器：*十二指腸炎、胃炎、膵炎（1.3%）

*筋骨格系及び結合組織：*関節炎、筋炎、リウマチ性多発筋痛、多発性筋炎、横紋筋融解症

*その他（血液／免疫）：*再生不良性貧血、結膜炎、血球減少症（2.5%）、好酸球増加症（2.1%）、多形紅斑、組織球性壊死性リンパ節炎（菊池リンパ節炎）、過敏性血管炎、髄膜炎、感音性聴力低下、乾癬、サルコイドーシス、全身性炎症反応症候群、実質臓器移植拒絶反応

5.2 注入に伴う反応

重度の注入に伴う反応が YERVOY で発現する可能性がある。重度又は生命を脅かす注入に伴う反応を示す患者では YERVOY を中止すること。軽度又は中等度の注入に伴う反応を示す患者には中断又は注入速度を落とすこと。*［用法・用量（2.3）参照］*切除不能又は転移性悪性黒色腫の治療のため YERVOY 3 mg/kg の単剤投与を受けた患者の 0.6%（3/511 例）に注入に伴う反応が発現した。RCC 又は mCRC の治療として YERVOY 1 mg/kg と nivolumab の併用投与を受けた患者の 5%（33/666 例）に注入に伴う反応が認められた。HCC の治療のため YERVOY 3 mg/kg と nivolumab の併用投与を受けた患者の 8%（4/49 例）に注入に伴う反応が発現した。注入に伴う反応は、YERVOY 1 mg/kg を 6 週間間隔、nivolumb 3 mg/kg を 2 週間間隔で併用投与した悪性胸膜中皮腫患者の 12%（37/300 例）に発現した。

5.3 YERVOY 投与後の同種造血幹細胞移植の合併症

同種造血幹細胞移植（HSCT）の前後に YERVOY を投与された患者では、致命的又は重篤な移植片対宿主病（GVHD）が発生する可能性がある。これらの合併症は、CTLA-4 受容体遮断抗体と同種 HSCT との間で介入療法を行っても発現する可能性がある。

	GVHD の証拠を得るために患者を注意深く観察し、異常が認められた場合には適切な処置を行うこと。［*副作用（6.2）参照*］また、HSCT の施行後に YERVOY を投与する場合は，YERVOY による治療のリスクベネフィットを慎重に検討すること。 **5.4 胚-胎児毒性** その作用機序及び動物試験から得られた調査結果に基づくと、妊婦に投与された場合、YERVOY は胎児に害を及ぼす可能性がある。動物生殖試験では、カニクイザルに器官形成期開始時から分娩まで ipilimumab を投与したところ、流産、死産及び早産（それに伴う出生体重の低下）の発現率が上昇し、乳児死亡率が用量依存的に増加した。Ipilimumab の作用は妊娠中期及び後期で高いと考えられる。妊婦には、胎児に対する潜在的リスクを伝えること。生殖能がある女性には、YERVOY の投与中及び最終投与から 3 ヵ月間は有効な避妊法を使用するよう助言すること*［特別な患者集団での使用（8.1, 8.3）参照］*。 **5.5 Nivolumab との併用におけるリスク** YERVOY は、進行性 RCC、MSI-H 又は dMMR mCRC、HCC 及び NSCLC 患者に対する nivolumab との併用を適応とする。併用療法に適用される追加のリスク情報については、nivolumab の添付文書を参照のこと。
副作用	以下の臨床的に重要な副作用は、添付文書の他項に記載されている： • 重度及び致死性の免疫介在性副作用*［警告及び使用上の注意（5.1）参照］* • 注入に伴う反応*［警告及び使用上の注意（5.2）参照］*。 **6.1 臨床試験での経験** 臨床試験は多様な条件下で実施されるため、ある薬剤の臨床試験で認められた副作用の発現率を別の薬剤の臨床試験で認められた発現率と直接比較することはできず、臨床現場で認められる発現率を反映していない可能性がある。 警告及び使用上の注意の項に記載されているデータは、MDX010-20 試験の患者 511 例における YERVOY 3 mg/kg の単剤投与（又は開発中の gp100 ペプチドワクチンとの併用投与）、CHECKMATE-214、CHECKMATE-142、CHECKMATE-227 及び CHECKMATE-743 の患者 1,362 例における YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用投与、CHECKMATE-067、CHECKMATE-040 及び別の無作為化試験の患者 456 例における YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用投与、CHECKMATE-9LA における YERVOY 1 mg/kg と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法の併用投与を反映している。 <u>切除不能又は転移性悪性黒色腫</u> MDX010-20 試験では、前治療歴を有する切除不能又は転移性悪性黒色腫患者 643 例を対象に YERVOY の安全性を評価した。*［臨床試験（14.1）参照］* MDX010-20 試験では、活動性の自己免疫疾患患者又は臓器移植時の全身免疫抑制療法を施行中の患者は除外された。YERVOY 3 mg/kg を単剤として 4 回静脈内投与（131 例）、YERVOY と開発中の gp100 ペプチドワクチンを併用投与（380 例）、又は gp100 ペプチドワクチンを単剤投与した（132 例）。本試験の患者への投与回数の中央値は 4 回（範囲：1～4 回）であった。 試験の患者集団特性：年齢の中央値は 57 歳（範囲：19～90）、男性の割合は 59%、白人の割合は 94%、ベースライン ECOG パフォーマンスステータスが 0 の割合は 56%であった。 患者の 10%が副作用のために YERVOY の投与を中止した。MDX010-20 試験の副作用を表 4 に示す。

表 4：MDX010-20 試験で gp100 ペプチドワクチンと比較した YERVOY 投与患者における特定の副作用（≥5%）（全 Grade で群間差 5%超、Grade 3～5 で群間差 1%超）

副作用	YERVOY 3 mg/kg 131 例		YERVOY 3 mg/kg 及び gp100 380 例		gp100 132 例	
	全 Grade (%)	Grade 3～5 (%)	全 Grade (%)	Grade 3～5 (%)	全 Grade (%)	Grade 3～5 (%)
一般・全身および投与部位の状態						
疲労	41	7	34	5	31	3
胃腸						
下痢	32	5	37	4	20	1
大腸炎	8	5	5	3	2	0
皮膚						
そう痒症	31	0	21	<1	11	0
発疹	29	2	25	2	8	0

切除不能又は転移性黒色腫：nivolumab との併用投与

CHECKMATE-067（無作為化（1:1:1）、二重盲検試験）の未治療の切除不能又は転移性の悪性黒色腫患者 937 例を対象に nivolumab との併用投与又は単剤投与における YERVOY の安全性を評価した*［臨床試験（14.1）参照］*。試験では自己免疫疾患を有する患者、治験薬の投与開始前 14 日以内にコルチコステロイド（プレドニゾン換算で 10 mg/日を超える用量）又はその他の全身性免疫抑制療法を必要とする状態である患者、B 型肝炎、C 型肝炎の検査陽性の患者、又は HIV 感染の既往のある患者は除外した。

患者は以下の投与群に無作為に割り付けられた:

- YERVOY 3 mg/kg を 90 分かけて点滴静注し、nivolumab 1 mg/kg を 3 週間間隔で 4 回点滴静注した後、nivolumab 3 mg/kg を単剤として 2 週間間隔で点滴静注する（YERVOY と nivolumab 投与群;313 例）
- Nivolumab 3 mg/kg を 2 週間間隔で点滴静注する（nivolumab 群;313 例）
- YERVOY 3 mg/kg を 90 分かけて 3 週間間隔で 4 回点滴静注する（YERVOY 群;311 例）

YERVOY と nivolumab 投与群の nivolumab の投与期間の中央値は、2.8 カ月（範囲:1 日~36.4 ヵ月）であった。投与期間は患者の 39%で 6 ヵ月以上、30%で 1 年超であった。

YERVOY と nivolumab の投与を受けた患者において、重篤な副作用は 74%で認められた。副作用のため患者の 47%が投与を中止し、58%が投与を延期し、72%に Grade 3 又は Grade 4 の副作用が発現した。

YERVOY と nivolumab 投与群において最も高頻度（10%以上）に認められた重篤な副作用は、下痢（13%）、大腸炎（10%）及び発熱（10%）であった。YERVOY 群

及び nivolumab 群において最も高頻度に認められた両薬剤の中止に至った副作用は、大腸炎（10%）、下痢（8%）、 ALT 増加（4.8%）、 AST 増加（4.5%）及び肺臓炎（1.9%）であった。

YERVOY と nivolumab 投与群において最も高頻度（20%以上）に認められた副作用は、疲労、下痢、発疹、悪心、発熱、そう痒症、筋骨格痛、嘔吐、食欲減退、咳嗽、頭痛、呼吸困難、上気道感染、関節痛及びトランスアミナーゼ上昇であった。

本剤の副作用及び臨床検査値異常の発現状況は表 5 及び表 6 のとおりであった。

表 5：CHECKMATE-067 試験で YERVOY と nivolumab 投与群又は nivolumab 群の 10%以上の患者に生じ、YERVOY 群よりも発現率が高かった副作用（全 Grade で群間差 5%以上、Grade 3～4 で群間差 2%以上）

副作用	YERVOY と Nivolumab (n=313)		Nivolumab (n=313)		YERVOY (n=311)	
	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)
一般						
疲労 [a]	62	7	59	1.6	51	4.2
発熱	40	1.6	16	0	18	0.6
消化器						
下痢	54	11	36	5	47	7
悪心	44	3.8	30	0.6	31	1.9
嘔吐	31	3.8	20	1.0	17	1.6
皮膚および皮下組織障害						
発疹 [b]	53	6	40	1.9	42	3.5
白斑	9	0	10	0.3	5	0
筋骨格系および結合組織						
筋骨格痛 [c]	32	2.6	42	3.8	36	1.9
関節痛	21	0.3	21	1.0	16	0.3
代謝および栄養						
食欲減退	29	1.9	22	0	24	1.3
呼吸器、胸郭および縦隔						
咳嗽/湿性咳嗽	27	0.3	28	0.6	22	0
呼吸困難/労作性呼吸困難	24	2.9	18	1.3	17	0.6
感染症						
上気道感染 [d]	23	0	22	0.3	17	0
内分泌						
甲状腺機能低下症	19	0.6	11	0	5	0
甲状腺機能亢進症	11	1.3	6	0	1	0
臨床検査						
体重減少	12	0	7	0	7	0.3
血管						
高血圧 [e]	7	2.2	11	5	9	2.3

毒性は NCI CTCAE v4 により Grade づけした

[a] 無力症及び疲労を含む。
[b] 膿疱性皮疹、皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、アトピー性皮膚炎、水疱性皮膚炎、剥脱性皮膚炎、乾癬様皮膚炎、薬疹、剥脱性皮疹、紅斑性皮疹、全身性皮疹、斑状皮疹、斑状丘疹状皮疹、麻疹様皮疹、丘疹状皮疹、丘疹鱗屑性皮疹及びそう痒性皮疹を含む。
[c] 背部痛、骨痛、筋骨格系胸痛、筋骨格系不快感、筋肉痛、頚部痛、四肢痛及び脊椎痛を含む。
[d] 上気道感染、鼻咽頭炎、咽頭炎及び鼻炎を含む。
[e] 高血圧及び血圧上昇を含む。

YERVOY と nivolumab との併用投与を受けた患者の 10%未満に認められた臨床的に重要な副作用:

胃腸障害:口内炎、腸管穿孔

皮膚および皮下組織障害:白斑

筋骨格系および結合組織障害:ミオパチー、シェーグレン症候群、脊椎関節症、筋炎（多発性筋炎を含む）

神経系障害:神経炎、腓骨神経麻痺

表 6: CHECKMATE-067 試験で YERVOY と nivolumab の併用投与又は nivolumab の単剤投与を受けた患者の 20%以上に生じ、YERVOY 群よりも発現率が高かったベースライン [a] からの臨床検査値異常の悪化（全 Grade で群間差 5%以上、Grade 3～4 で群間差 2%以上）

臨床検査値異常	YERVOY と Nivolumab		Nivolumab		YERVOY	
	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)
化学検査						
ALT 増加	55	16	25	3.0	29	2.7
高血糖	53	5	46	7	26	0
AST 増加	52	13	29	3.7	29	1.7
低ナトリウム血症	45	10	22	3.3	26	7
リパーゼ増加	43	22	32	12	24	7
アルカリホスファターゼ増加	41	6	27	2.0	23	2.0
低カルシウム血症	31	1.1	15	0.7	20	0.7
アミラーゼ増加	27	10	19	2.7	15	1.6
クレアチニン増加	26	2.7	19	0.7	17	1.3
血液学的検査						
貧血	52	2.7	41	2.6	41	6
リンパ球減少症	39	5	41	4.9	29	4.0

[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に少なくとも 1 回測定された臨床検査値の両方を有する患者数に基づく:YERVOY

と nivolumab 併用（範囲:75~297 例）; nivolumab（範囲:81~306 例）; YERVOY（範囲:61~301 例）

悪性黒色腫における術後補助療法

完全切除されたリンパ節転移陽性の皮膚黒色腫患者を対象とした非盲検、多施設共同、無作為化試験である E1609 において、YERVOY の安全性を評価した。*［臨床試験（14.2）参照］*YERVOY 3 mg/kg を 3 週間ごとに 4 回静脈内投与し、その後 3 mg/kg を 12 週間ごとに最大 4 回追加投与、又は高用量インターフェロンα2b（HDI）を投与した。患者の 55%が 6 ヵ月以上、42%が 1 年を超えて YERVOY の投与を受けた。

YERVOY の投与を受けた患者の 1.4%に致死的な副作用が発現し、これらの事象には胃穿孔（0.2%）及び心停止（0.2%）が含まれた。副作用のため患者の 35%が YERVOY の投与を中止した。

YERVOY 群において最も高頻度（20%以上）に認められた副作用は、疲労、下痢、発疹、そう痒症、悪心及び頭痛であった。E1609 試験の副作用を表 7 に示す。

表 7：E1609 試験において、YERVOY3 mg/kg の投与を受けた患者に発現した副作用（≥10%）

副作用	YERVOY 3 mg/kg n=516		HDI n=520	
	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)
一般・全身および投与部位の状態				
疲労	56	3	87	22
食欲減退	14	0.6	53	2.1
発熱	10	0	31	0.8
胃腸				
下痢	49	10	34	0.8
悪心	29	1.2	66	4.2
腹痛	19	1	9	0.4
嘔吐	11	0.6	26	2.3
大腸炎	10	8	1	0.4
皮膚				
発疹	46	4	18	1
そう痒症	41	2	15	0
神経系障害				
頭痛	25	2	45	3
内分泌				
内分泌障害、他	19	4.1	2	0

甲状腺機能低下症	11	0.6	10	0.2
副腎機能不全	10	2	0.6	0

他の臨床成績

YERVOY を 0.3～10 mg/kg の用量範囲で単剤投与した複数の臨床試験全体では、以下の副作用も報告された（特に明記する場合を除き、発現率 1%未満）：蕁麻疹（2%）、大腸潰瘍、食道炎、急性呼吸窮迫症候群、腎不全及び infusion reaction。

進行腎細胞癌: nivolumab との併用投与

CHECKMATE-214 では、未治療の進行 RCC 患者 1082 例を対象に YERVOY と nivolumab の併用投与の安全性を評価した。*［臨床成績（14.3）を参照］* YERVOY 1 mg/kg と nivolumab 3 mg/kg の併用を 3 週ごとに 4 回静脈内投与し、その後 nivolumab 単剤を 3 mg/kg の投与量で 2 週ごとに投与（n=547）、又はスニチニブ 50 mg/日を各 6 週間サイクルの最初の 4 週間経口投与（n=535）した。治療期間の中央値は YERVOY と nivolumab の併用投与群で 7.9 ヶ月（範囲：1 日～21.4 ヶ月以上）であった。本試験では、YERVOY 及び nivolumab の併用投与群の患者の 57%が 6 ヶ月超の治療を受け、患者の 38%が 1 年超の治療を受けた。

重篤な副作用は YERVOY と nivolumab の併用投与を受けた患者の 59%に発現した。YERVOY と nivolumab の併用投与の治療を受けた患者の 2%以上で報告された最も高頻度の重篤な副作用は、下痢、発熱、肺炎、肺臓炎、下垂体炎、急性腎障害、呼吸困難、副腎機能不全、および大腸炎であった。

YERVOY と nivolumab の併用投与を受けた患者では、治験薬の投与中止に至った副作用の発現率は 31%、投与延期に至った副作用の発現率は 54%であった。

YERVOY と nivolumab の併用投与群で最もよく見られた副作用（20%以上）は、疲労、発疹、下痢、筋骨格痛、そう痒症、悪心、咳嗽、発熱、関節痛、および食欲減退であった。CHECKMATE-214 の副作用を表 8 に要約する。

表 8：CHECKMATE-214 で YERVOY と nivolumab の併用投与を受けた患者に発現した副作用（>15%）

副作用	YERVOY 1 mg/kg と Nivolumab （n=547）		スニチニブ （n=535）	
	Grade 1～4 (%)	Grade 3～4 (%)	Grade 1～4 (%)	Grade 3～4 (%)
一般・全身状態および投与部位の状態				
疲労 [a]	58	8	69	13
発熱	25	0.7	17	0.6
浮腫 [b]	16	0.5	17	0.6
皮膚および皮下組織				
発疹 [c]	39	3.7	25	1.1
そう痒症／全身性そ	33	0.5	11	0

う痒症				
消化器				
下痢	38	4.6	58	6
悪心	30	2.0	43	1.5
嘔吐	20	0.9	28	2.1
腹痛	19	1.6	24	1.9
便秘	17	0.4	18	0
筋骨格系および結合組織				
筋骨格痛 [d]	37	4.0	40	2.6
関節痛	23	1.3	16	0
呼吸器、胸郭および縦隔障害				
咳嗽／湿性咳嗽	28	0.2	25	0.4
呼吸困難／労作性呼吸困難	20	2.4	21	2.1
代謝および栄養				
食欲減退	21	1.8	29	0.9
神経系				
頭痛	19	0.9	23	0.9
内分泌				
甲状腺機能低下症	18	0.4	27	0.2

毒性は NCI CTCAE v4 により Grade づけした。

[a] 無力症を含む。
[b] 末梢性浮腫、末梢腫脹を含む。
[c] ざ瘡様皮膚炎、水疱性皮膚炎、剥脱性皮膚炎、薬疹、剥脱性発疹、紅斑性皮疹、毛孔性皮疹、全身性皮疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹、膿疱性皮疹、固定薬疹を含む。
[d] 背部痛、骨痛、筋骨格系胸痛、筋骨格不快感、筋肉痛、頚部痛、四肢痛、脊椎痛を含む。

CHECKMATE-214 の臨床検査値異常を表 9 に要約する。

表 9：CHECKMATE-214 で YERVOY と nivolumab の併用投与を受けた患者におけるベースラインからの臨床検査値異常の悪化（>15%）

臨床検査値異常	YERVOY 1 mg/kg と Nivolumab[a]		スニチニブ [a]	
	Grade 1～4 (%)	Grade 3～4 (%)	Grade 1～4 (%)	Grade 3～4 (%)
血液生化学的検査				

リパーゼ増加	48	20	51	20
クレアチニン増加	42	2.1	46	1.7
ALT 増加	41	7	44	2.7
AST 増加	40	4.8	60	2.1
アミラーゼ増加	39	12	33	7
低ナトリウム血症	39	10	36	7
アルカリホスファターゼ増加	29	2.0	32	1.0
高カリウム血症	29	2.4	28	2.9
低カリウム血症	21	0.4	35	0.6
低マグネシウム血症	16	0.4	26	1.6
血液学的検査				
貧血	43	3.0	64	9
リンパ球減少症	36	5	63	14

[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に少なくとも 1 回測定された臨床検査値の両方を有する患者数に基づく：YERVOY と nivolumab 併用投与群（範囲：490～538 例）およびスニチニブ群（範囲：485～523 例）。

ベースライン時に TSH が ULN 以下の患者では、スニチニブ群（61%）と比較して、YERVOY と nivolumab 併用投与群（31%）で試験治療中に TSH が ULN よりも上昇した患者の割合が小さかった。

MSI-High 又は dMMR の転移性結腸・直腸癌

MSI-H 又は dMMR mCRC の治療: nivolumab との併用投与

免疫療法未治療の MSI-H 又は dMMR mCRC 患者を対象とした無作為化、非盲検、3 群比較試験である CHECKMATE-8HW において、YERVOY と nivolumab 併用投与の安全性を評価した。*［臨床試験（14.4）参照］*患者は以下のいずれかの治療を受けた。

- 3 週間間隔で YERVOY 1 mg/kg と nivolumab 240 mg を最大 4 回併用投与した後、nivolumab 480 mg を 4 週間間隔で投与。
- 2 週間間隔で nivolumab 240 mg を 6 回投与した後、nivolumab 480 mg を 4 週間間隔で投与。
- 治験担当医師が選択した化学療法：mFOLFOX 又は FOLFIRI *［臨床試験（14.4）参照］*。

YERVOY と nivolumab 併用群における YERVOY への曝露期間中央値は 2.1 ヵ月（範囲：1 日～3.7 ヵ月）であり、投与回数の中央値は 4 回（範囲：1～4 回）であった。YERVOY と nivolumab 併用群における投与期間中央値は 20.5 ヵ月（範囲：1 日～35.9 ヵ月）であり、70%が 6 ヵ月超、63%が 1 年超の曝露期間であった。Nivolumab 単剤投与群における投与期間中央値は 16.4 ヵ月（範囲：1 日～36 ヵ月）であり、64%が 6 ヵ月超、54%が 1 年超の曝露期間であった。

重大な副作用は、YERVOY と nivolumab 併用投与を受けた患者の 46%、nivolumab 単剤投与を受けた患者の 39%に発現した。YERVOY と nivolumab 併用投与を受けた患者の 1%以上で報告された最も頻繁に認められた重大な副作用は、副腎機能不全（2.8%）、下垂体炎（2.8%）、下痢（2.0%）、腹痛（2.0%）、小腸閉塞（2.0%）、肺炎（1.7%）、急性腎障害（1.4%）、免疫性腸炎（１.4%）、肺臓炎（1.4%）、大腸炎（1.1%）、大腸閉塞（1.1%）および尿路感染（1.1%）であった。OPDIVO 単剤投与を受けた患者の 1%超で報告された最も頻繁に認められた重篤な副作用は、腸閉塞（2.3%）、急性腎障害（1.7%）、COVID-19（1.7%）、腹痛（1.4%）、下痢（1.4%）、イレウス（1.4%）、亜イレウス（1.4%）、肺塞栓症（1.4%）、副腎機能不全（1.1%）及び肺炎（1.1%）であった。

YERVOY と nivolumab の併用投与を受けた 2 例（0.6%）に致死的な副作用が発現し、これらの事象には心筋炎及び肺臓炎（各 1 例）が含まれた。

YERVOY および／又は nivolumab の投与で、併用投与を受けた患者の 19%が投与を中止した。投与中止に至った主な副作用（1%超）は、副腎機能不全（1.4%）、免疫性腸炎（1.1%）及び肺臓炎（1.1%）であった。Nivolumab 単剤投与を受けた患者の 13%が投与を中止した。副作用のため、YERVOY および／又は nivolumab 併用投与を受けた患者の 48%が投与を中断し、nivolumab 単剤投与を受けた患者の 37%が投与を中断した。

YERVOY と nivolumab の併用投与を受けた患者の 20%以上で報告された最も一般的な副作用は、疲労、下痢、そう痒症、腹痛、筋骨格痛および悪心であった。
Nivolumab 単剤投与を受けた患者の 20%以上で報告された最も一般的な副作用は、疲労、下痢、腹痛、そう痒症および筋骨格痛であった。

表 10 および表 11 にそれぞれ CHECKMATE-8HW の YERVOY と nivolumab 併用群と nibolumab 群における副作用および臨床検査値異常を要約する。

表 10：患者の≥10%で発現し、全グレードで>5%の群間差が認められた副作用（CHECKMATE-8HW）

副作用	YERVOY と Nivolumab（n=352）		Nivolumab（n=351）	
	全 Grade (%)	Grade 3 又は 4 (%)	全 Grade (%)	Grade 3 又は 4 (%)
消化器				
下痢 [a]	35	4.5	30	3.4
皮膚および皮下組織				
そう痒症	30	0	23	0
筋骨格系および結合組織				
関節痛	20	0.6	15	0.6
内分泌				
甲状腺機能低下症	18	0.6	10	0
甲状腺機能亢進症	12	0	5	0

毒性グレードは、NCI CTCAE v5 に基づく。

[a] 大腸炎、下痢、腸炎、免疫性腸炎を含む。

表 11：患者の≥10%で発現し、全グレードで>5%の群間差が認められたベースライン[a]からの臨床検査値異常（CHECKMATE-8HW）

臨床検査値異常	YERVOY と Nivolumab（n=352）		Nivolumab（n=351）	
	全 Grade (%)	Grade 3 又は 4 (%)	全 Grade (%)	Grade 3 又は 4 (%)
血液学的検査				
リンパ球減少	30	5	37	4
好中球減少	21	1.7	12	0.6
生化学検査				
リパーゼ増加	44	10	32	11
アミラーゼ増加	41	4.6	33	5
ALT 増加	39	3.5	32	1.4
AST 増加	38	3.2	29	1.4
ナトリウム減少	36	3.2	30	2.3
クレアチニン増加	32	2	25	1.4
カリウム増加	29	1.2	35	0.9
ブドウ糖減少	17	0	12	0

[a] 各検査値異常の発現率は、ベースライン時及び試験中少なくとも 1 回の臨床検査値の測定値の両方を有している患者数に基づく。：YERVOY と nivolumab 併用群（範囲：108～343 例）及び nibolumab 単剤投与群（範囲：102～348 例）

肝細胞癌: nivolumab との併用投与

切除不能又は転移性肝細胞癌（HCC）

切除不能又は転移性 HCC の成人患者を対象とした無作為化、非盲検試験である CHECKMATE-9DW において、YERVOY と nivolumab を併用投与したときの安全性を評価した。*［臨床試験（14.5）参照］*YERVOY と nivolumab（332 例）又は治験担当医師が選択したレンバチニブ（275 例）又はソラフェニブ（50 例）を以下の用量で投与した。

- 3 週間間隔で YERVOY 3 mg/kg を 30 分かけて点滴静注と nivolumab 1 mg/kg を 30 分かけて点滴静注を最大 4 回併用投与した後、nivolumab 480 mg を 4 週間間隔で 30 分かけて点滴静注で単剤投与した。又は
- 治験責任医師の選択により
  - レンバチニブ 8 mg を 1 日 1 回経口投与（体重 60 kg 未満の場合）又は 12 mg を 1 日 1 回経口投与（体重 60 kg 以上の場合）又は
  - ソラフェニブ 400 mg を 1 日 2 回経口投与

YERVOY、nivolumab 併用群における nivolumab の曝露期間中央値は 4.7 ヵ月（範囲：0.1 ヵ月未満～24.4 ヵ月）、45%が 6 ヵ月超、30%が 1 年超の曝露期間であった。

YERVOY と nivolumab の併用投与を受けた患者の 53%に重篤な副作用が発現した。2%以上で最も頻繁に報告された肝臓関連以外の重篤な副作用は下痢／大腸炎（4.5%）、胃腸出血（3%）及び発疹（2.4%）であった。YERVOY と nivolumab の併用投与を受けた患者の 17%に肝臓関連の重篤な副作用が発現し、そのうち 16%にグレード 3~4 の事象が発現した。患者の 1%以上で報告されたグレードを問わない主な重篤な副作用は免疫性肝炎（3%）、AST/ALT 増加（3%）、肝不全（2.4%）、腹水（2.4%）及び肝毒性（1.2%）であった。

YERVOY と nivolumab の併用投与を受けた 12 例（3.6%）に致死的な副作用が発現し、このうち 4 例（1.2%）は免疫介在性又は自己免疫性肝炎、4 例（1.2%）は肝不全により死亡した。

副作用のため YERVOY と nivolumab の併用投与を受けた患者の 27%が投与を中止した。1%を超える患者で投与中止に至った副作用は、免疫性肝炎（1.8%）、下痢／大腸炎（1.8%）及び肝不全（1.2%）であった。

副作用のため YERVOY と nivolumab の併用投与を受けた患者の 62%が投与を中断した。5%を超える患者で投与中断を要した副作用は AST 増加（13%）、ALT 増加(11%)及び下痢／大腸炎（8%）であった。

主な副作用（20%超）は発疹、そう痒症、疲労、及び下痢であった。

表 12 および表 13 に、それぞれ CHECKMATE-9DW における副作用及び臨床検査値異常を要約する。

表 12：CHECKMATE-9DW で YERVOY と nivolumab の併用投与を受けた患者の 10%以上に発現した副作用

副作用	YERVOY と Nivolumab (n=332)		レンバチニブ又はソラフェニブ (n=325)	
	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)
皮膚および皮下組織				
発疹 [a]	36	3.6	15	1.2
そう痒症	34	1.5	7	0.3
一般				
疲労 [a]	33	2.4	39	4
発熱 [a]	15	0.6	9	1.5
浮腫 [a]	13	1.2	13	1.5
胃腸				
下痢	25	6	39	3.4
腹痛 [a]	14	1.2	27	2.5
悪心	10	0.3	16	0.9
筋骨格系および結合組織				
筋骨格痛 [a]	17	0.6	23	0.3
関節痛	12	0.3	13	0.6
代謝および栄養				
食欲減退	16	1.2	28	1.8

内分泌				
甲状腺機能低下症 [a]	14	0	27	0
甲状腺機能亢進症	11	0.6	1.5	0
呼吸、胸部、および縦隔				
咳嗽 [a]	13	0	8	0

毒性グレードは、NCI CTCAE v5 に基づく。
[a] 複数の関連する用語の複合を表す。

YERVOY と nivolumab の併用投与を受けた患者の 10%未満で報告された臨床的に重要な副作用は、高血糖（8%）、副腎機能不全（4.2%）、肺臓炎（2.7%）、及び膵炎（2.4%）であった。

表 13：CHECKMATE-9DW で YERVOY と nivolumab の併用投与を受けた患者の 20%以上に生じたベースライン [a] からの臨床検査値の悪化

臨床検査値異常	YERVOY と Nivolumab（n=332）		レンバチニブ又はソラフェニブ（n=325）	
	Grade 1～4 (%)	Grade 3～4 (%)	Grade 1～4 (%)	Grade 3～4 (%)
血液生化学的検査				
AST 増加	62	29	51	14
ALT 増加	61	17	46	9
リパーゼ増加	58	16	39	5
アルブミン減少	48	0.9	57	0.6
低ナトリウム血症	45	6	42	3.8
高血糖	44	15	32	2.1
ビリルビン増加	44	10	44	8
アミラーゼ増加	41	6	26	1
アルカリホスファターゼ増加	36	1.2	38	5
低カルシウム血症	29	0.9	46	0
クレアチニン増加	26	2.4	23	0.6
低カリウム血症	21	2.1	20	2.6
血液学的検査				
貧血	44	5	40	3.8
リンパ球減少症	40	6.1	40	8
血小板減少症	27	4	44	4.8
好中球減少症	24	4	32	3.5

[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に少なくとも 1 回測定された臨床検査値の両方を有する患者数に基づく:YERVOY と

nivolumab 併用（範囲：168～331 例）及びレンバチニブ又はソラフェニブ（範囲：145～315 例）

治療歴のある肝細胞癌

CHECKMATE-040 のコホート 4 に組み入れられたソラフェニブ投与中に進行した又はソラフェニブ不耐となった Child-Pugh 分類 A の肝硬変を伴う HCC 患者 49 例の部分集団において、YERVOY 3 mg/kg と nivolumab 1 mg/kg 併用投与の安全性を評価した。YERVOY 及び nivolumab を 3 週間間隔で 4 回投与し、その後疾患進行又は許容できない毒性の発現まで nivolumab 240 mg を 2 週間間隔で単剤投与した。

YERVOY と nivolumab の併用投与中、49 例中 33 例（67%）が YERVOY と nivolumab の予定された 4 回の投与をすべて受けた。全投与期間における YERVOY 投与期間の中央値は 2.1 ヵ月（範囲：0～4.5 ヵ月）、nivolumab 投与期間の中央値は 5.1 ヵ月（範囲：0～35 ヵ月以上）であった。投与期間は患者の 47%で 6 ヵ月超、35%で 1 年超であった。重篤な副作用は 59%で認められた。副作用のため患者の 29%が投与を中止し、65%が投与を延期した。

患者の 4%以上で報告された重篤な副作用は、発熱、下痢、貧血、AST 増加、副腎機能不全、腹水、食道静脈瘤出血、低ナトリウム血症、血中ビリルビン増加及び肺臓炎であった。

CHECKMATE-040 における YERVOY と nivolumab 併用投与時の副作用を表 14 に、臨床検査値異常を表 15 に要約する。

表 14： CHECKMATE-040 のコホート 4 で YERVOY と nivolumab の併用投与を受けた患者の 10%以上で発現した副作用

副作用	YERVOY 及び Nivolumab (n=49)	
	全 Grade（%）	Grade3～4（%）
皮膚および皮下組織		
発疹	53	8
そう痒症	53	4
筋骨格系および結合組織		
筋骨格痛	41	2
関節痛	10	0
胃腸		
下痢	39	4
腹痛	22	6
悪心	20	0
腹水	14	6
便秘	14	0
口内乾燥	12	0
消化不良	12	2
嘔吐	12	2
口内炎	10	0

	呼吸器、胸郭および縦隔		
	咳嗽	37	0
	呼吸困難	14	0
	肺臓炎	10	2
	代謝および栄養		
	食欲減退	35	2
	一般・全身		
	疲労	27	2
	発熱	27	0
	倦怠感	18	2
	浮腫	16	2
	インフルエンザ様疾患	14	0
	悪寒	10	0
	神経系		
	頭痛	22	0
	浮動性めまい	20	0
	内分泌		
	甲状腺機能低下症	20	0
	副腎機能不全	18	4
	臨床検査		
	体重減少	20	0
	精神		
	不眠症	18	0
	血液およびリンパ系		
	貧血	10	4
	感染症		
	インフルエンザ	10	2
	血管		
	低血圧	10	0

YERVOY と nivolumab の併用投与を受けた患者の 10%未満で報告された臨床的に重要な副作用は、高血糖（8%）、大腸炎（4%）及び血中クレアチンホスホキナーゼ増加（2%）であった。

表 15： CHECKMATE-040 のコホート 4 で YERVOY と nivolumab の併用投与を受けた患者におけるベースラインから悪化した特定の臨床検査値異常（10%以上）

臨床検査値異常	YERVOY 及び Nivolumab（n=47）	
	全 Grade（%）	Grade3～4（%）
血液検査		
リンパ球減少症	53	13
貧血	43	4.3
好中球減少症	43	9
白血球減少症	40	2.1
血小板減少症	34	4.3
生化学検査		
AST 増加	66	40
ALT 増加	66	21
ビリルビン増加	55	11
リパーゼ増加	51	26
低ナトリウム血症	49	32
低カルシウム血症	47	0
アルカリホスファターゼ増加	40	4.3
アミラーゼ増加	38	15
低カリウム血症	26	2.1
高カリウム血症	23	4.3
クレアチニン増加	21	0
低マグネシウム血症	11	0

YERVOY と nivolumab の併用投与を受けた患者では、ベースライン時に活動性 HBV 又は HCV を有していた患者のそれぞれ 28 例中 4 例（14%）及び 4 例中 2 例（50%）でウイルス学的ブレークスルーが認められた。HBV のウイルス学的ブレークスルーは、ベースライン時に HBV DNA が検出された患者で、HBV DNA が 1 log 以上増加した場合と定義した。HCV のウイルス学的ブレークスルーは、ベースラインからの HCV RNA の 1 log の増加と定義した。

転移性 NSCLC の一次治療：nivolumab との併用投与

EGFR 又は ALK 遺伝子変異を有さない未治療の転移性又は再発性 NSCLC 患者を対象とした無作為化、多施設共同、複数コホート、非盲検試験である CHECKMATE-227 において YERVOY を nivolumab と併用投与したときの安全性を評価した。*［臨床試験（14.6）参照］*同試験では、未治療の脳転移、癌性髄膜炎、活動性自己免疫疾

患、又は全身免疫抑制療法を要する疾患を有する患者を除外した。患者には 6 週間間隔で YERVOY 1 mg/kg を 30 分かけて点滴静注及び 2 週間間隔で nivolumab 3 mg/kg を 30 分かけて点滴静注、又は 3 週間間隔でプラチナ製剤を含む 2 剤併用化学療法を 4 サイクル投与した。YERVOY 及び nivolumab 投与患者における投与期間の中央値は 4.2 ヵ月（範囲：1 日～25.5 ヵ月）であり、YERVOY 及び nivolumab の投与期間は患者の 39%で 6 ヵ月超、23%で 1 年超であった。人口統計学的特性は以下のとおりであった：年齢中央値 64 歳（範囲：26～87）、48%が 65 歳以上、76%が白人、67%が男性。ベースラインの ECOG パフォーマンスステータスは 0（35%）又は 1（65%）であり、85%が元／現喫煙者、11%で脳転移、28%で扁平上皮癌、72%で非扁平上皮癌の組織像が認められた。

重篤な副作用は 58%で認められた。副作用のため患者の 24%が YERVOY 及び nivolumab の投与を中止し、53%が投与を 1 回以上中断した。

主な重篤な副作用（2%以上）は、肺炎、下痢／大腸炎、肺臓炎、肝炎、肺塞栓症、副腎機能不全及び下垂体炎であった。致死的な副作用が患者の 1.7%に発現した。これらの事象には、肺臓炎（4 例）、心筋炎、急性腎障害、ショック、高血糖、多臓器不全及び腎不全が含まれた。主な副作用（20%以上）は、疲労、発疹、食欲減退、筋骨格痛、下痢／大腸炎、呼吸困難、咳嗽、肝炎、悪心及びそう痒症であった。

表 16 及び表 17 に、それぞれ CHECKMATE-227 における特定の副作用及び臨床検査値異常を要約する。

表 16： YERVOY と nivolumab の投与を受けた患者の 10%以上に発現した副作用 CHECKMATE-227

副作用	YERVOY 及び Nivolumab（n=576）		プラチナ製剤を含む 2 剤併用化学療法（n=570）	
	全 Grade（%）	Grade3～4（%）	全 Grade（%）	Grade3～4（%）
一般・全身				
疲労 [a]	44	6	42	4.4
発熱	18	0.5	11	0.4
浮腫 [b]	14	0.2	12	0.5
皮膚および皮下組織				
発疹 [c]	34	4.7	10	0.4
そう痒症 [d]	21	0.5	3.3	0
代謝および栄養				
食欲減退	31	2.3	26	1.4
筋骨格系および結合組織				
筋骨格痛 [e]	27	1.9	16	0.7
関節痛	13	0.9	2.5	0.2
胃腸				
下痢／大腸炎 [f]	26	3.6	16	0.9
悪心	21	1.0	42	2.5

便秘	18	0.3	27	0.5
嘔吐	13	1.0	18	2.3
腹痛 [g]	10	0.2	9	0.7
呼吸器、胸郭および縦隔				
呼吸困難 [h]	26	4.3	16	2.1
咳嗽 [i]	23	0.2	13	0
肝胆道系				
肝炎 [j]	21	9	10	1.2
内分泌				
甲状腺機能低下症 [k]	16	0.5	1.2	0
甲状腺機能亢進症 [l]	10	0	0.5	0
感染症および寄生虫症				
肺炎 [m]	13	7	8	4.0
神経系				
頭痛	11	0.5	6	0

[a] 疲労及び無力症を含む。
[b] 眼瞼浮腫、顔面浮腫、全身性浮腫、限局性浮腫、浮腫、末梢性浮腫、及び眼窩周囲浮腫を含む。
[c] 自己免疫性皮膚炎、皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、アトピー性皮膚炎、水疱性皮膚炎、接触皮膚炎、剥脱性皮膚炎、乾癬様皮膚炎、肉芽腫性皮膚炎、全身性皮疹、薬疹、異汗性湿疹、湿疹、剥脱性皮疹、結節性皮疹、発疹、紅斑性皮疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹、膿疱性皮疹及び中毒性皮疹を含む。
[d] そう痒症及び全身性そう痒症を含む。
[e] 背部痛、骨痛、筋骨格系胸痛、筋骨格系不快感、筋骨格痛、筋肉痛及び四肢痛を含む。
[f] 大腸炎、顕微鏡的大腸炎、潰瘍性大腸炎、下痢、感染性腸炎、腸炎、感染性小腸結腸炎及びウイルス性腸炎を含む。
[g] 腹部不快感、腹痛、下腹部痛、上腹部痛及び腹部圧痛を含む。
[h] 呼吸困難及び労作性呼吸困難を含む。
[i] 咳嗽及び湿性咳嗽を含む。
[j] アラニンアミノトランスフェラーゼ増加、アスパラギン酸アミノトランスフェラーゼ増加、自己免疫性肝炎、血中ビリルビン増加、肝酵素上昇、肝不全、肝機能異常、肝炎、E 型肝炎、肝細胞損傷、肝毒性、高ビリルビン血症、免疫性肝炎、肝機能検査異常、肝機能検査値上昇及びトランスアミナーゼ上昇を含む。
[k] 自己免疫性甲状腺炎、血中甲状腺刺激ホルモン増加、甲状腺機能低下症、原発性甲状腺機能低下症、甲状腺炎及び遊離トリヨードチロニン減少を含む。
[l] 血中甲状腺刺激ホルモン減少、甲状腺機能亢進症、遊離トリヨードチロニン増加を含む。
[m] 下気道感染、細菌性下気道感染、肺感染、肺炎、アデノウイルス性肺炎、誤嚥性肺炎、細菌性肺炎、クレブシエラ菌性肺炎、インフルエンザ性肺炎、ウイルス性肺炎、異型肺炎、器質化肺炎を含む。

CHECKMATE-227 におけるその他の臨床的に重要な副作用：

皮膚および皮下組織：蕁麻疹、脱毛症、多形紅斑、尋常性白斑

胃腸：口内炎、膵炎、胃炎

筋骨格系および結合組織：関節炎、リウマチ性多発筋痛、横紋筋融解症

神経系：末梢性ニューロパチー、自己免疫性脳炎

血液およびリンパ系：好酸球増加症

眼障害：霧視、ぶどう膜炎

心臓：心房細動、心筋炎

表 17： YERVOY と nivolumab の投与を受けた患者の 20%以上に発現したベースライン[a]からの臨床検査値の悪化 - CHECKMATE-227

臨床検査値異常	YERVOY 及び Nivolumab		プラチナ製剤を含む 2 剤併用化学療法	
	Grade 1～4 (%)	Grade 3～4 (%)	Grade 1～4 (%)	Grade 3～4 (%)
血液検査				
貧血	46	3.6	78	14
リンパ球減少症	46	5	60	15
生化学検査				
低ナトリウム血症	41	12	26	4.9
AST 増加	39	5	26	0.4
ALT 増加	36	7	27	0.7
リパーゼ増加	35	14	14	3.4
アルカリホスファターゼ増加	34	3.8	20	0.2
アミラーゼ増加	28	9	18	1.9
低カルシウム血症	28	1.7	17	1.3
高カリウム血症	27	3.4	22	0.4
クレアチニン増加	22	0.9	17	0.2

[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に少なくとも 1 回測定された臨床検査値の両方を有する患者数に基づく：YERVOY 及び nivolumab 投与群（範囲：494～556 例）及び化学療法群（範囲：469～542 例）

<u>転移性又は再発性 NSCLC の一次治療：nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法との併用投与</u>

CHECKMATE-9LA において YERVOY を nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法と併用したときの安全性を評価した。*［臨床試験（14.6）参照］*患者には 6 週間間隔で YERVOY 1 mg/kg と 3 週間間隔で nivolumab 360 mg 及び 3 週間間隔でプラチナ製剤を含む 2 剤併用化学療法を 2 サイクルを併用投与、又は 3 週間間隔でプラチナ製剤を含む 2 剤併用化学療法を 4 サイクルを投与した。YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法の併用投与期間の中央値は 6 ヵ

月（範囲：1 日～19 ヵ月）であり、YERVOY 及び nivolumab の投与期間は患者の 50%で 6 ヵ月超、13%で 1 年超であった。

YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法との併用投与を受けた患者の 57%に重篤な副作用が発現した。主な重篤な副作用（2%超）は、肺炎、下痢、発熱性好中球減少症、貧血、急性腎障害、筋骨格痛、呼吸困難、肺臓炎、及び呼吸不全であった。致死的な副作用は 7 例（2%）に発現し、その内訳は肝毒性、急性腎不全、敗血症、肺臓炎、低カリウム血症を伴う下痢、及び血小板減少症に伴う大量の喀血であった。

副作用のため患者の 24%が YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法との併用投与を中止し、56%が投与を 1 回以上中断した。主な副作用（20%以上）は、疲労、筋骨格痛、悪心、下痢、発疹、食欲減退、便秘、及びそう痒症であった。

表 18 及び表 19 に、それぞれ CHECKMATE-9LA における特定の副作用及び臨床検査値異常を要約する。

表 18： YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法の投与を受けた患者の 10%超に発現した副作用 - CHECKMATE-9LA

副作用	YERVOY と Nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法（n=358）		プラチナ製剤を含む 2 剤併用化学療法（n=349）	
	全 Grade（%）	Grade3～4（%）	全 Grade（%）	Grade3～4（%）
一般・全身				
疲労[a]	49	5	40	4.9
発熱	14	0.6	10	0.6
筋骨格系および結合組織				
筋骨格痛[b]	39	4.5	27	2.0
胃腸				
悪心	32	1.7	41	0.9
下痢[c]	31	6	18	1.7
便秘	21	0.6	23	0.6
嘔吐	18	2.0	17	1.4
腹痛[d]	12	0.6	11	0.9
皮膚および皮下組織				
発疹[e]	30	4.7	10	0.3
そう痒症[f]	21	0.8	2.9	0
脱毛症	11	0.8	10	0.6
代謝および栄養				
食欲減退	28	2.0	22	1.7
呼吸器、胸郭および縦隔				
咳嗽[g]	19	0.6	15	0.9

呼吸困難[h]	18	4.7	14	3.2
内分泌				
甲状腺機能低下症[i]	19	0.3	3.4	0
神経系				
頭痛	11	0.6	7	0
浮動性めまい[j]	11	0.6	6	0

NCI CTCAE v4 に従って毒性を Grade 分類した。

[a] 疲労及び無力症を含む。
[b] 筋肉痛、背部痛、四肢痛、筋骨格痛、骨痛、側腹部痛、筋痙縮、筋骨格系胸痛、筋骨格障害、骨炎、筋骨格硬直、非心臓性胸痛、関節痛、関節炎、関節障害、関節滲出液、乾癬性関節症、滑膜炎を含む。
[c] 大腸炎、潰瘍性大腸炎、下痢及び腸炎を含む。
[d] 腹部不快感、腹痛、下腹部痛、上腹部痛及び消化器痛を含む。
[e] ざ瘡、皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、アトピー性皮膚炎、水疱性皮膚炎、全身性剥脱性皮膚炎、湿疹、膿漏性角皮症、手掌・足底発赤知覚不全症候群、発疹、紅斑性皮疹、全身性皮疹、斑状皮疹、斑状丘疹状皮疹、麻疹様発疹、丘疹性皮疹、そう痒性皮疹、皮膚剥脱、皮膚反応、皮膚毒性、スティーブンス・ジョンソン症候群、蕁麻疹を含む。
[f] そう痒症及び全身性そう痒症を含む。
[g] 咳嗽、湿性咳嗽及び上気道咳症候群を含む。
[h] 呼吸困難、安静時呼吸困難及び労作性呼吸困難を含む。
[i] 自己免疫性甲状腺炎、血中甲状腺刺激ホルモン増加、甲状腺機能低下症、甲状腺炎及び遊離トリヨードサイロニン減少を含む。
[j] 浮動性めまい、回転性めまい及び頭位性回転性めまいを含む。

表 19： YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法の投与を受けた患者の 20%超に発現したベースライン[a]からの臨床検査値の悪化 - CHECKMATE-9LA

臨床検査値異常	YERVOY と Nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法		プラチナ製剤を含む 2 剤併用化学療法	
	Grade1～4 (%)	Grade3～4 (%)	Grade1～4 (%)	Grade3～4 (%)
血液検査				
貧血	70	9	74	16
リンパ球減少症	41	6	40	11
好中球減少症	40	15	42	15
白血球減少症	36	10	40	9
血小板減少症	23	4.3	24	5
生化学検査				
高血糖	45	7	42	2.6
低ナトリウム血症	37	10	27	7
ALT 増加	34	4.3	24	1.2

リパーゼ増加	31	12	10	2.2
アルカリホスファターゼ増加	31	1.2	26	0.3
アミラーゼ増加	30	7	19	1.3
AST 増加	30	3.5	22	0.3
低マグネシウム血症	29	1.2	33	0.6
低カルシウム血症	26	1.4	22	1.8
クレアチニン増加	26	1.2	23	0.6
高カリウム血症	22	1.7	21	2.1

[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に測定された臨床検査値の両方を有する患者数（YERVOY+nivolumab+プラチナ製剤を含む 2 剤併用化学療法群［範囲:197～347 例］及びプラチナ製剤を含む 2 剤併用化学療法群［範囲：191～335 例］）に基づく。

切除不能な悪性胸膜中皮腫の一次治療：nivolumab との併用投与

未治療の切除不能な悪性胸膜中皮腫患者を対象とした無作為化、非盲検試験である CHECKMATE-743 において YERVOY を nivolumab と併用したときの安全性を評価した。*［臨床試験（14.7）参照］*患者には 6 週間隔で YERVOY 1 mg/kg を 30 分かけて点滴静注及び 2 週間間隔で nivolumab 3 mg/kg を 30 分かけて点滴静注を最長 2 年間まで、又はプラチナ製剤を含む 2 剤併用化学療法を最大 6 サイクル投与した。
YERVOY と nivolumab 併用療法の投与期間の中央値は 5.6 ヵ月（範囲：0 ヵ月～26.2 ヵ月）であり、YERVOY 及び nivolumab の投与期間は患者の 48%で 6 ヵ月超、24%で 1 年超であった。

YERVOY と nivolumab の併用投与を受けた患者の 54%に重篤な副作用が発現した。主な重篤な副作用（2%以上）は、肺炎、発熱、下痢、肺臓炎、胸水、呼吸困難、急性腎不全、注入に伴う反応、筋骨格痛及び肺塞栓症であった。致命的な副作用は 4 例（1.3%）に発現し、その内訳は肺臓炎、急性心不全、敗血症及び脳炎であった。

副作用のため患者の 23%が YERVOY と nivolumab の併用投与を中止し、52%が投与を 1 回以上中断した。さらに、副作用のため患者の 4.7%が YERVOY のみ投与を中止した。

主な副作用（20%以上）は疲労、筋骨格痛、発疹、下痢、呼吸困難、悪心、食欲減退、咳嗽及びそう痒症であった。

CHECKMATE-743 の副作用及び臨床検査値異常を表 20 及び表 21 に示す。

表 20: YERVOY と nivolumab の投与を受けた患者の 10%以上に発現した副作用 - CHECKMATE-743

副作用	YERVOY と Nivolumab (n=300)		化学療法 (n=284)	
	全 Grade (%)	Grade3~4 (%)	全 Grade (%)	Grade3~4 (%)
一般・全身				
疲労 [a]	43	4.3	45	6
発熱 [b]	18	1.3	4.6	0.7
浮腫 [c]	17	0	8	0

筋骨格系および結合組織				
筋骨格痛[d]	38	3.3	17	1.1
関節痛	13	1.0	1.1	0
皮膚および皮下組織				
発疹[e]	34	2.7	11	0.4
そう痒症[f]	21	1.0	1.4	0
胃腸				
下痢[g]	32	6	12	1.1
悪心	24	0.7	43	2.5
便秘	19	0.3	30	0.7
腹痛[h]	15	1	10	0.7
嘔吐	14	0	18	2.1
呼吸器、胸郭および縦隔				
呼吸困難[i]	27	2.3	16	3.2
咳嗽[j]	23	0.7	9	0
代謝および栄養				
食欲減退	24	1.0	25	1.4
内分泌				
甲状腺機能低下症[k]	15	0	1.4	0
感染症および寄生虫症				
上気道感染[l]	12	0.3	7	0
肺炎[m]	10	4.0	4.2	2.1

[a] 疲労及び無力症を含む
[b] 発熱及び腫瘍熱を含む
[c] 浮腫、全身性浮腫、末梢性浮腫及び末梢性腫脹を含む
[d] 筋骨格痛、背部痛、骨痛、側腹部痛、不随意性筋収縮、筋痙縮、筋攣縮、筋骨格系胸痛、筋骨格硬直、筋肉痛、頚部痛、非心臓性胸痛、四肢痛、リウマチ性多発筋痛及び脊髄痛を含む
[e] 発疹、ざ瘡、ざ瘡様皮膚炎、アレルギー性皮膚炎、アトピー性皮膚炎、自己免疫性皮膚炎、水疱性皮膚炎、接触性皮膚炎、皮膚炎、薬疹、異汗性湿疹、湿疹、紅斑性皮疹、剥脱性皮疹、全身性剥脱性皮膚炎、全身性皮疹、肉芽腫性皮膚炎、膿皮症、斑状皮疹、斑状丘疹状皮疹、麻疹様皮疹、丘疹性皮疹、乾癬様皮膚炎、そう痒性皮疹、膿疱性皮疹、皮膚剥脱、皮膚反応、皮膚毒性、スティーブンス・ジョンソン症候群、中毒性皮疹、蕁麻疹を含む
[f] そう痒症、アレルギー性そう痒症、全身性そう痒症を含む
[g] 下痢、大腸炎、腸炎、感染性腸炎、腸炎、感染性腸炎、顕微鏡的大腸炎、潰瘍性大腸炎及びウイルス性腸炎を含む
[h] 腹痛、腹部不快感、腹部圧痛、胃腸痛、下腹部痛及び上腹部痛を含む
[i] 呼吸困難、安静時呼吸困難及び労作性呼吸困難を含む
[j] 咳嗽、湿性咳嗽及び上気道咳嗽症候群を含む

[k] 甲状腺機能低下症、自己免疫性甲状腺炎、遊離トリヨードチロニン減少、血中甲状腺刺激ホルモン増加、原発性甲状腺機能低下症、甲状腺炎及び自己免疫性甲状腺機能低下症を含む
[l] 上気道感染、鼻咽頭炎、咽頭炎及び鼻炎を含む
[m] 肺炎、下気道感染、肺感染、誤嚥性肺炎、ニューモシスチス・イロベチイ肺炎を含む

表 21: YERVOY と nivolumab の併用投与を受けた患者の 20%以上に発現したベースライン[a] からの臨床検査値の悪化 - CHECKMATE-743

臨床検査値異常	YERVOY と Nivolumab		化学療法	
	Grade1~4 (%)	Grade3~4 (%)	Grade1~4 (%)	Grade3~4 (%)
生化学検査				
高血糖	53	3.7	34	1.1
AST 増加	38	7	17	0
ALT 増加	37	7	15	0.4
リパーゼ増加	34	13	9	0.8
低ナトリウム血症	32	8	21	2.9
アルカリホスファターゼ増加	31	3.1	12	0
高カリウム血症	30	4.1	16	0.7
低カルシウム血症	28	0	16	0
アミラーゼ増加	26	5	13	0.9
クレアチニン増加	20	0.3	20	0.4
血液検査				
リンパ球減少症	43	8	57	14
貧血	43	2.4	75	15

[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に少なくとも 1 回測定された臨床検査値の両方を有する患者数（YERVOY+nivolumab 群［範囲:109～297 例］及び化学療法群［範囲：90～276 例］）に基づく

<u>切除不能進行又は転移性の ESCC の一次治療：nivolumab との併用投与</u>

未治療の切除不能な進行、再発又は転移性の ESCC 患者を対象とした無作為化、実薬対照、多施設共同、非盲検試験である CHECKMATE-648 において、YERVOY と nivolumab と併用したときの安全性を評価した*［臨床試験（14.8）参照］*。患者は以下のいずれかの治療を受けた。

- 6 週間間隔で YERVOY 1 mg/kg、2 週間間隔で nivolumab 3 mg/kg を併用投与。
- 5-FU（フルオロウラシル）800 mg/m^2/day を Day 1 から Day 5 まで静脈内投与し、シスプラチン 80 mg/m^2 を Day 1 に静脈内投与（4 週間を 1 サイクルとする）

YERVOY と nivolumab を併用投与された患者における曝露期間中央値は 2.8 ヵ月（範囲：0～24 ヵ月）であった。YERVOY と nivolumab の併用投与を受けた患者の 69%に重篤な副作用が発現した。

YERVOY と nivolumab の併用投与を受けた患者の 2%以上で報告された主な重篤な副作用は肺炎（10%）、発熱（4.3%%）、肺臓炎（4.0%）、誤嚥性肺炎（3.7%）、嚥下障害（3.7%）、肝機能異常（2.8%）、食欲減退（2.8%）、副腎機能不全（2.5%）、及び脱水（2.5%）であった。

YERVOY と nivolumab の併用投与を受けた 5 例（1.6%）に致死的な副作用が発現し、これらの事象には肺臓炎、間質性肺疾患、肺塞栓症及び急性呼吸窮迫症候群が含まれた。

副作用のため、患者の 23%が YERVOY 及び／又は nivolumab の投与を中止し、46%が投与を中断した。

YERVOY と nivolumab の併用投与を受けた患者の 20%以上で発現した主な副作用は発疹、疲労、発熱、悪心、下痢、及び便秘であった。

表 22 及び表 23 に、それぞれ CHECKMATE-648 における副作用及び臨床検査値異常を要約する。

表 22：CHECKMATE-648 で YERVOY と nivolumab の併用投与を受けた患者の 10%以上に発現した副作用

副作用	YERVOY と Nivolumab（n=322）		シスプラチンと 5-FU（n=304）	
	全 Grade (%)	Grade 3～4 (%)	全 Grade (%)	Grade 3～4 (%)
皮膚および皮下組織				
発疹 [a]	31	3.1	7	0
そう痒症	17	0.9	3.6	0
一般				
疲労 [c]	28	2.5	41	4.9
発熱 [b]	23	0.9	12	0.3
胃腸				
悪心	22	0.6	56	2.6
下痢	22	1.9	20	2.0
便秘	20	0.3	43	1.0
嘔吐	15	1.6	19	3.0
嚥下障害	12	5	12	4.9
口内炎 [d]	11	0.6	35	3.0
腹痛 [e]	10	0.9	11	0.7
代謝及び栄養				
食欲減退	17	4.0	50	6
筋骨格系および結合組織				
筋骨格痛 [f]	14	0.6	8	0.3
感染症及び寄生虫症				
肺炎 [g]	14	8	10	2.6
内分泌				

甲状腺機能低下症	14	0	0.3	0
呼吸、胸部、および縦隔				
咳嗽 [h]	13	0.3	13	0.3
臨床検査				
体重減少	12	1.9	11	1.0

毒性グレードは、NCI CTCAE v4 に基づく。

[a] 皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、水疱性皮膚炎、薬疹、剥脱性皮疹、紅斑性皮疹、毛孔性皮疹、斑状皮疹、斑状丘疹状皮疹及びそう痒性皮疹を含む
[b] 腫瘍熱を含む
[c] 無力症及び倦怠感を含む
[d] アフタ性潰瘍、口腔内潰瘍及び粘膜の炎症を含む
[e] 腹部不快感、下腹部痛及び上腹部痛を含む
[f] 背部痛、骨痛、筋骨格系胸痛、筋肉痛、頚部痛、四肢痛及び脊椎痛を含む
[g] 器質化肺炎、細菌性肺炎及びシュードモナス菌性肺炎を含む
[h] 湿性咳嗽を含む

表 23：CHECKMATE-648 で YERVOY と nivolumab の併用投与を受けた患者の 10%以上に生じたベースライン [a] からの臨床検査値の悪化

臨床検査値異常	YERVOY と Nivolumab（n=322）		シスプラチンと 5-FU（n=304）	
	Grade 1～4 (%)	Grade 3～4 (%)	Grade 1～4 (%)	Grade 3～4 (%)
血液学的検査				
貧血	52	7	66	14
リンパ球減少症	50	13	44	8
好中球減少症	13	1.3	48	13
血小板減少症	12	1.0	29	2.8
生化学検査				
低ナトリウム血症	45	11	40	8
高血糖	43	4.3	36	0.8
AST 増加	39	6	11	1.4
ALT 増加	33	6	8	0.7
低カルシウム血症	32	0	23	0.7
アルカリホスファターゼ増加	31	3.3	15	0
高カリウム血症	23	1.6	24	0.7
低カリウム血症	19	5	17	6
高カルシウム血症	15	2.0	8	0
低血糖	15	1.2	7	0
クレアチニン増加	15	0.7	31	0.7
低マグネシウム血症	15	0	25	1.8

	[a] 各検査値異常の発現率は、ベースライン時に測定された臨床検査値及び治験期間中に少なくとも 1 回測定された臨床検査値の両方を有する患者数に基づく:YERVOY と nivolumab 併用（範囲：59～307 例）及びシスプラチンと 5-FU（範囲：59～283 例） **6.2 市販後の経験** YERVOY の承認後使用では、以下の副作用が特定されている。これらの副作用は規模が不明な母集団に由来する自発的な報告であるため、必ずしもその頻度を確実に推定できる、あるいは薬剤曝露との因果関係を確立できるとは限らない。 *血液およびリンパ系障害*：血球貪食性リンパ組織球症（HLH） *免疫系*：移植片対宿主病、実質臓器移植拒絶反応 *皮膚および皮下組織*：好酸球増加と全身症状を伴う薬物反応（DRESS 症候群）
薬物相互作用	なし
特定の集団における使用	**8.1 妊娠** リスクの概要 動物試験から得られた調査結果及びその作用機序に基づくと*［臨床薬理（12.1）参照］*、妊婦に投与された場合、YERVOY は胎児に害を及ぼす可能性がある。妊婦における YERVOY 曝露に関する臨床データは不十分である。動物生殖試験では、カニクイザルに器官形成期開始時から分娩まで ipilimumab を投与したところ、流産、死産及び早産（それに伴う出生体重の低下）の発現率が上昇し、乳児死亡率が用量依存的に増加した*（データ参照）*。Ipilimumab の作用は妊娠中期及び後期で高いと考えられる。ヒト IgG1 は胎盤関門を通過することが知られており、ipilimumab は IgG1 である。したがって、ipilimumab は母親から胎児に移行する可能性がある。妊婦には、胎児に対する潜在的リスクを伝えること。妊娠をブリストル・マイヤーズスクイブ（1-844-593-7869）に報告すること。 米国の一般母集団で臨床的に認識された主な先天異常及び流産の推定背景リスクは、それぞれ 2%～4%、15%～20%である。 データ *動物データ* 胚・胎児発生と周産期及び出生後の発生の複合試験では、妊娠カニクイザルに妊娠初期の器官形成期開始時から分娩まで 3 週間ごとに ipilimumab を投与した。妊娠初期及び中期に、生殖に対する投与に関連した有害作用は認められなかった。Ipilimumab の投与はヒトでの臨床用量である ipilimumab 3 mg/kg での曝露量の約 2.6 から 7.2 倍となる曝露レベルであり、妊娠後期から、流産、死産及び早産（それに伴う出生体重の低下）が用量依存的に上昇し、及び乳児死亡率が上昇した。加えて、子宮内で ipilimumab 30 mg/kg（3 mg/kg 投与時の曲線下面積に基づくヒト曝露量の 7.2 倍）に曝露された幼齢サル 2 例の泌尿生殖器系に発生異常がみられた。幼齢雌サル 1 例では左腎及び尿管の一側性先天性腎無形成、幼齢雄サル 1 例では尿道閉鎖とそれに伴う尿路閉塞及び陰嚢浮腫が認められた。 遺伝子操作により作製された、ipilimumab の標的である CTLA-4 のヘテロ接合マウス（CTLA-4+/−）は健康と考えられ、出生児は健康な CTLA-4+/−ヘテロ接合体マウスであった。交配させた CTLA-4+/−ヘテロ接合体マウスの出生児は CTLA-4 欠損（負のホモ接合体、CTLA-4−/−）マウスであった。CTLA-4−/−負のホモ接合体である出生児は健康と思われたが、2 週齢までに多臓器のリンパ増殖性疾患の徴候を示し、広範囲のリンパ増殖と多臓器の組織破壊により 3～4 週齢までに全て死亡した。

8.2 授乳

リスクの概要

YERVOY の母乳移行、並びに授乳中の小児又は乳汁産生に対する YERVOY の影響に関するデータはない。サルでは、ipilimumab は乳汁中に移行した。*（データ参照）* 授乳中の小児に重篤な副作用が発現する可能性があるため、YERVOY の投与中及び最終投与後 3 ヵ月間は授乳しないよう指導すること。

データ

ヒトでの推奨用量における曝露量の 2.6 及び 7.2 倍の曝露量となる用量を投与されたサルでは、ipilimumab が 0.1 及び 0.4 mcg/mL の濃度で乳汁中に認められ、血清中薬物濃度の最大約 0.3%であった。

8.3 生殖能のある女性及び男性

妊娠検査

YERVOY の投与開始前に、妊娠可能な女性の妊娠の有無を確認すること。*［特別な集団への投与（8.1）参照］*

避妊

妊婦に投与された場合、YERVOY は胎児に害を及ぼす可能性がある*［特定の集団における使用（8.1）参照］* 生殖能がある女性には、YERVOY の投与中及び最終投与から 3 ヵ月間は有効な避妊法を使用するよう指導すること。

8.4 小児等への投与

YERVOY の安全性および有効性は、12 歳以上の小児患者において、切除不能又は転移性黒色腫の単剤及び nivolumab との併用療法、MSI-H 又は dMMR を有する切除不能又は転移性 CRC に対する nivolumab との併用療法及びフルオロピリミジン、オキサリプラチンおよびイリノテカンによる治療後に進行した MSI-H 又は dMMR mCRC の nibolumab との併用療法について確立されている。これらの適応症に対する YERVOY の使用は、悪性黒色腫又は MSI-H 又は dMMR mCRC の成人患者を対象とした YERVOY の適切な対照試験からのエビデンス、そして、小児患者を対象とした追加の薬物動態データによって裏付けられている。12 歳以上の小児患者における ipilimumab の曝露量は成人患者と同等であり、悪性黒色腫及び MSI-H 又は dMMR mCRC の経過は、12 歳以上の小児患者と成人患者において類似しているため、安全性及び有効性を外挿することができる。*［副作用（6.1）、臨床薬理（12.3）、臨床試験（14.4）参照］*

切除不能又は転移性悪性黒色腫、MSI-H 又は dMMR mCRC の 12 歳未満の小児患者における YERVOY の有効性及び安全性は確立されていない。

小児患者の安全性と有効性は、悪性黒色腫の術後補助療法又は進行性腎細胞癌、肝細胞癌、転移性非小細胞性肺癌、悪性胸膜中皮腫及び食道癌の治療に対しては確立されていない。

用量設定試験（NCT01445379）では、切除不能な IIIc 期又は IV 期の悪性黒色腫（12 例）、進行性又は難治性の肉腫（17 例）、腎又は膀胱癌（3 例）及び神経芽細胞腫（1 例）を含む再発性又は難治性固形腫瘍を有する 2 歳から 21 歳（中央値 13 歳）の小児患者 33 例が検討された。本試験では、悪性黒色腫以外の固形癌患者で奏功は確認されず、小児患者に新たな安全性シグナルは認められなかった。

8.5 高齢者への投与

単剤

	MDX010-20（切除不能又は転移性悪性黒色腫）試験において、YERVOY 3 mg/kg を投与された患者 511 例のうち、28%は 65 歳以上であった。これらの患者と若年患者の間で安全性又は有効性の全体的な差はなかった。 Nivolumab との併用投与 CHECKMATE-067 試験において YERVOY と nivolumab との併用投与に無作為割付された患者 314 例のうち、41%が 65 歳以上、11%が 75 歳以上であった。これらの患者と若年患者の間で安全性又は有効性の全体的な差は報告されなかった。 CHECKMATE-227（NSCLC）において、6 週間間隔で YERVOY 1 mg/kg 及び 2 週間間隔で nivolumab 3 mg/kg 投与に無作為割付された患者 576 例のうち、48%が 65 歳以上、10%が 75 歳以上であった。安全性に関して高齢患者と若年患者の間で全体的な差は報告されなかったが、75 歳以上の患者（29%）では、YERVOY と nivolumab の併用投与を受けた全患者（18%）と比較して、副作用による投与中止率が高かった。CHECKMATE-227 において 6 週間間隔で YERVOY 1 mg/kg 及び 2 週間間隔で nivolumab 3 mg/kg 投与に無作為割付された主要有効性集団（PD-L1≥1%）の患者 396 例中、全生存期間のハザード比は 65 歳未満の患者 199 例で 0.70（95% CI: 0.55, 0.89）、65 歳以上の患者 197 例で 0.91（95% CI: 0.72, 1.15）であった。 *［臨床試験（14.6）参照］* CHECKMATE-743（悪性胸膜中皮腫）において、6 週間間隔で YERVOY 1 mg/kg と 2 週間間隔で nivolumab 3 mg/kg の併用投与に無作為割付された 303 例のうち、77%が 65 歳以上、26%が 75 歳以上であった。安全性に関して高齢患者と若年患者の間で全体的な差は報告されなかったが、75 歳以上の患者では、重篤な副作用の発現率及び副作用による投与中止率（それぞれ 68%及び 35%）が YERVOY と nivolumab の併用投与を受けたすべての患者（それぞれ 54%及び 28%）と比較して高かった。化学療法を受けた 75 歳以上の患者では、重篤な副作用の発現率は 34%であり、副作用による投与中止率が 26%であったのに対し、すべての患者ではそれぞれ 28%及び 19%であった。YERVOY と nivolumab との併用に無作為化された患者の全生存期間のハザード比は 65 歳未満の患者 71 例では 0.76（95% CI:0.52, 1.11）であったのに対し、65 歳以上の患者 232 例では 0.74（95% CI:0.59, 0.93）であった。 CHECKMATE-214（腎細胞癌）で YERVOY 1 mg/kg と nivolumab との併用投与に無作為割付された患者 550 例のうち、38%が 65 歳以上、8%が 75 歳以上であった。これらの患者と若年患者との間の安全性について、全体的な相違はなかった。中等度～高リスクの高齢患者で、有効性についての全体的な相違はなかった。 YERVOY と nivolumab の併用投与に無作為割付された dMMR 又は MSI-H 転移性 CRC（mCRC）患者 354 例のうち、44%が 65 歳以上、14%が 75 歳以上であった。Nivolumab 単剤投与に無作為割付された 353 例のうち、45%が 65 歳以上、13%が 75 歳以上であった。YERVOY と nivolumab の併用投与を受けた 65 歳以上の患者におけるグレード 3 又はグレード 4 の副作用の発現率（55%）は、65 歳未満の患者（42%）と比較して高かった。副作用による投与中止率は、YERVOY と nivolumab の併用投与を受けた 65 歳以上の患者（23%）が 65 歳未満の患者（15%）と比較して高かった。YERVOY と nivolumab の併用投与を受けた高齢患者と若年患者との間で、有効性に関する全体的な差は報告されなかった。 *［臨床試験（14.4）参照］* YERVOY と nivolumab との併用投与に無作為割付された切除不能な肝細胞癌患者 335 例のうち、52%が 65 歳以上、14%が 75 歳以上であった。高齢患者と若年患者との間で、安全性についての全体的な相違はなかった。 CHECKMATE-040（肝細胞癌）のコホート 4 において、YERVOY 3 mg/kg と nivolumab を併用投与された 49 例のうち、29%が 65 歳以上 74 歳以下、8%が 75 歳以上であった。YERVOY を nivolumab と併用投与した臨床試験では、65 歳以上の肝細

	胞癌患者数が不十分であったため、若年患者との反応の差を確認することはできなかった。 CHECKMATE-648（ESCC）において 6 週間間隔で YERVOY 1 mg/kg と 2 週間間隔で nivolumab 3 mg/kg を併用投与した 325 例のうち、43%が 65 歳以上、7%が 75 歳以上であった。安全性に関して高齢患者と若年患者の間で全体的な差は報告されなかったが、副作用による投与中止率が、75 歳以上の患者（38%）で YERVOY と nivolumab の併用投与を受けたすべての患者（23%）と比較して高かった。化学療法を受けた 75 歳以上の患者では、副作用による投与中止率は全体の 23%に対して 33%であった。 CA184-029（悪性黒色腫における術後補助療法治療）試験及び CHECKMATE-142 試験（結腸・直腸癌）には、若年の患者と反応が異なるかどうかを判断するのに十分な数の 65 歳以上の患者が登録されていなかった。 <u>Nivolumab とプラチナ製剤との併用投与</u> CHECKMATE-9LA（NSCLC）において、6 週間間隔で YERVOY 1 mg/kg と 3 週間間隔で nivolumab 360 mg 及びプラチナ製剤を含む 2 剤併用化学療法（2 サイクル）の併用投与に無作為割付された患者 361 例のうち、51%が 65 歳以上、10%が 75 歳以上であった。安全性に関して高齢患者と若年患者の間で全体的な差は報告されなかったが、75 歳以上の患者（43%）では、YERVOY と nivolumab 及び化学療法の併用投与を受けた全患者（24%）と比較して、副作用による投与中止率が高かった。75 歳以上の化学療法のみを受けた患者における副作用による投与中止率は 16%であったのに対し、全患者における投与中止率は 13%であった。全生存期間に関する最新の解析に基づくと、CHECKMATE-9LA において YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法との併用に無作為化された患者 361 例のうち、全生存期間に関するハザード比は 65 歳未満の患者 176 例で 0.61（95% CI: 0.47, 0.80）であったのに対し、65 歳以上の患者 185 例では 0.73（95% CI: 0.56, 0.95）であった。
過量投与	なし
添付文書の改訂年月日	2025 年 5 月

14 臨床試験

14.1 切除不能又は転移性悪性黒色腫

アルデスロイキン、ダカルバジン、テモゾロミド、フォテムスチン又はカルボプラチンのうち 1 種類以上による前治療歴を有する切除不能又は転移性悪性黒色腫患者に対する無作為化（3:1:1）、二重盲検、ダブルダミー試験（NCT00094653）である MDX010-20 試験において YERVOY の有効性を検討した。この HLA 遺伝子型は、研究用のペプチドワクチンの免疫提示を促進する。また、本試験では活動性の自己免疫疾患を有する患者又は臓器移植時の全身免疫抑制療法を施行中の患者は除外された。患者を YERVOY（3 mg/kg の用量で 3 週間ごとに 4 回静脈内投与）と開発中の不完全フロイントアジュバント含有ペプチドワクチン（gp100）（2 mg ペプチドを 3 週間ごとに 4 回深部皮下投与）の併用投与群、プラセボと gp100 2 mg を 3 週間ごとに 4 回深部皮下投与する群、又はプラセボと YERVOY を 3 mg/kg の用量で 3 週間ごとに 4 回静脈内投与する群に無作為に割り付けた。主要評価項目は、gp100 単独療法群と比較した YERVOY+gp100 投与群における全生存期間（OS）であっ

た。副次評価項目はYERVOY単独療法群と比較したYERVOY+gp100投与群のOS、gp100単独療法群と比較したYERVOY単独療法群のOS、Week 24の治験責任医師により評価された奏効率（BORR）の各試験群間の比較、奏効期間などであった。腫瘍縮小効果の評価は、12週目及び24週目、それ以降は3ヵ月ごとに実施した。12週目又は24週目に客観的腫瘍縮小効果が認められた患者は、それぞれ16週目又は28週目に効果の持続性を確認するための評価を受けた。

合計 676 例の患者を無作為に割り付けた。内訳は YERVOY 及び gp100 併用投与群に 403 例、YERVOY の単剤投与群に 137 例、gp100 の単剤投与群に 136 例であった。無作為化された患者のうち、YERVOY+gp100 投与群、YERVOY 単独療法群及び gp100 単独療法群の男性の割合はそれぞれ61%、59%及び54%であった。 29%が65歳以上、年齢の中央値は57歳、71%は病期がM1cであり、12%が前治療のある脳転移を有し、98%で ECOG パフォーマンスステータスが 0 及び 1 であった。また、23%にアルデスロイキンの投与歴があり、38%でLDH高値がみられた。いずれかのYERVOY投与群に無作為化された患者の 61%が計画された 4 回の投与を全て受けた。追跡期間の中央値は8.9ヵ月であった。

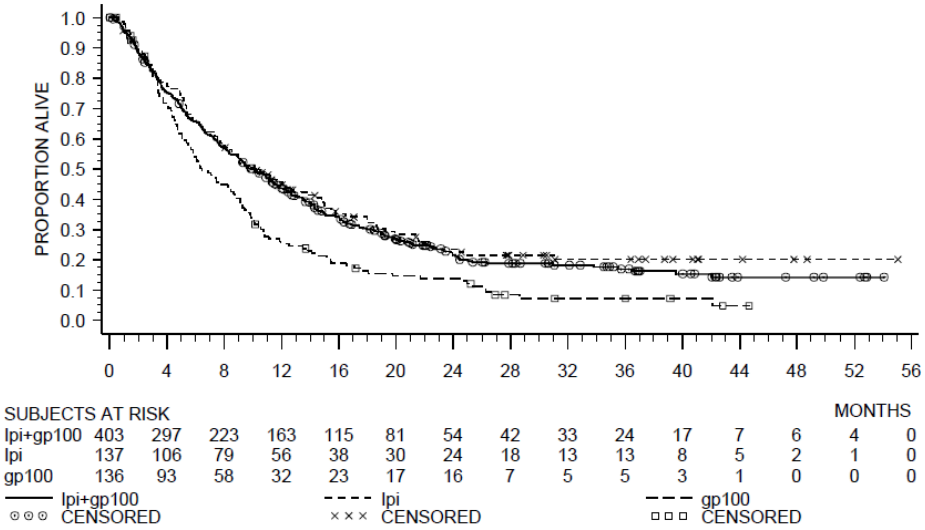
有効性の結果を表25及び図1に示す。

表 25：MDX010-20 試験における有効性の結果

	YERVOY 137 例	**YERVOY+gp100 403 例**	**gp100 136 例**
全生存期間			
中央値（月）（95% CI）	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)
ハザード比（対 gp100）（95% CI）	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
P 値	p=0.0026[a]	p=0.0004	
ハザード比（対 YERVOY）（95% CI）		1.04 (0.83, 1.30)	
最良総合効果率（BORR）（95% CI）	10.9% (6.3%, 17.4%)	5.7% (3.7%, 8.4%)	1.5% (0.2%, 5.2%)
奏効期間中央値（月）	NR[b]	11.5	NR[b]

[a] 多重比較の調整は行っていない。
[b] 未到達

図 1：MDX010-20 試験における全生存期間の Kaplan-Meier 曲線



<u>未治療の転移性悪性黒色腫: nivolumab との併用投与</u>

CHECKMATE-067（NCT01844505）は多施設共同無作為化（1:1:1）二重盲検試験であり、未治療の切除不能又は転移性悪性黒色腫患者 945 例を YERVOY と nivolumab（併用）群、nivolumab 群又は YERVOY 群のいずれかに無作為に割り付けた。患者は無作為化の 6 週間以上前に術後補助療法又は術前補助療法を完了し、抗 CTLA-4 抗体による治療歴がなく、活動性脳転移、眼内黒色腫、自己免疫疾患又は全身免疫抑制を要する医学的状態がないこととした。

患者は以下の投与群に無作為に割り付けられた:

- YERVOY 3 mg/kg と nivolumab 1 mg/kg を 3 週間間隔で 4 回点滴静注した後、nivolumab 3 mg/kg を単剤として 2 週間間隔で点滴静注する（YERVOY と nivolumab 群）
- Nivolumab 3 mg/kg を 2 週間間隔で点滴静注する（nivolumab 群）、又は
- YERVOY 3 mg/kg を 3 週間間隔で 4 回点滴静注した後、プラセボを 2 週間間隔で点滴静注する（YERVOY 群）

無作為化は、clinical trial assay で判定された PD-L 1 発現（腫瘍細胞膜発現が 5%以上 vs.5%未満）、BRAF V 600 変異の状態、AJCC 病期分類システムによる M ステージ（M0, M1a, M1b vs.M1c）により層別化した。無作為割付けの 12 週後、最初の 1 年は 6 週ごと、その後は 12 週ごとに腫瘍評価を実施した。主な有効性評価項目は、RECIST v 1.1 に基づく治験責任医師の評価による PFS 及び OS であった。その他の有効性評価項目は確定した ORR 及び奏効期間であった。

試験対象集団の特性：年齢中央値 61 歳（範囲：18~90）、男性 65%、白人 97%、ECOG パフォーマンススコア 0（73%）又は 1（27%）。疾患特性：AJCC 病期 IV 期（93%）;M1c 期（58%）、LDH 上昇（36%）、脳転移歴（4%）、BRAF V 600 変異陽性悪性黒色腫（32%）、clinical trial assay により判定した PD-L 1 腫瘍細胞膜発現が 5%以上（46%）;及び過去の術後補助療法（22%）。

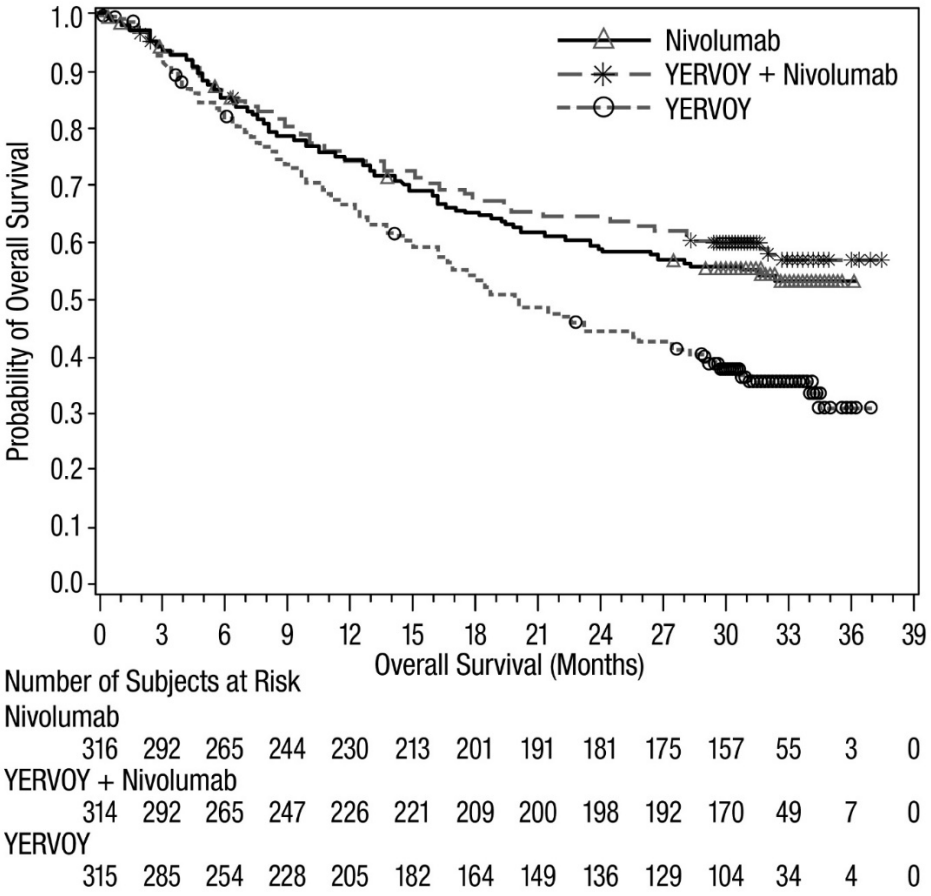
CHECKMATE-067 において、nivolumab を含むいずれかの投与群に無作為化された患者において、は YERVOY 群と比較して OS 及び PFS の統計学的に有意な改善を示した。本試験は、nivolumab に YERVOY を追加することにより、nivolumab 単剤療法と比較して PFS 又は OS が改善するかどうかを評価するようにデザインされていなかった。有効性の結果を表 26 及び図 2 に示す。

表 26: CHECKMATE-067 試験における有効性の結果

	YERVOY と Nivolumab (n=314)	**Nivolumab (n=316)**	**YERVOY (n=315)**
全生存率[a]			
死亡数 (%)	128 (41)	142 (45)	197 (63)
ハザード比[b] (対YERVOY) (95% CI)	0.55 (0.44, 0.69)	0.63 (0.50, 0.78)	
P値[c, d]	<0.0001	<0.0001	
無増悪生存期間[a]			
疾患進行又は死亡	151 (48%)	174 (55%)	234 (74%)
中央値 (月) (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
ハザード比[b] (対YERVOY) (95% CI)	0.42 (0.34, 0.51)	0.57 (0.47, 0.69)	
p-値[c, e]	<0.0001	<0.0001	
確定した奏効率[a]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-値[f]	<0.0001	<0.0001	
完全奏効	8.9%	8.5%	1.9%
部分奏効	41%	31%	12%
奏効期間			
奏効期間が≥6ヵ月の奏効例の割合	76%	74%	63%
範囲 (月)	1.2+ ~ 15.8+	1.3+ ~ 14.6+	1.0+ ~ 13.8+

[a] OS の結果は、最短追跡調査期間 28 ヵ月の OS の最終解析に基づいている。PFS（co-primary endpoint）及び ORR（secondary endpoint)）の結果は、最短追跡調査期間 9 ヵ月の主要解析に基づく
[b] 層別比例ハザードモデルに基づく
[c] 層別ログランク検定に基づく
[d] OS の p 値の最大値が 0.04（Hochberg 法で設定した有意水準）未満の場合、両方の p 値を有意とみなす
[e] 最終 PFS の治療比較のために、p 値を有意水準 0.005 と比較する。
[f] 層別 Cochran-Mantel-Haenszel 検定に基づく
+ 打ち切り観察

図 2: CHECKMATE-067 試験における全生存期間



48 ヵ月の最短追跡調査期間に基づく、YERVOY と nivolumab（併用）群における OS の中央値は未到達であった（95% CI：38.2, NR）。OS の中央値は nivolumab 群で 36.9 カ月（95% CI：28.3, NR）及び YERVOY 群で 19.9 カ月（95% CI：16.9, 24.6）であった。

28 ヵ月の最短追跡調査期間に基づく PFS の中央値は、YERVOY と nivolumab（併用）群で 11.7 ヵ月（95% CI：8.9, 21.9）、nivolumab 群で 6.9 ヵ月（95% CI：4.3, 9.5）、YERVOY 群で 2.9 ヵ月（95% CI：2.8, 3.2）であった。28 ヵ月の最短追跡調査期間に基づく、奏効が 24 ヵ月以上持続した被験者の割合は、YERVOY と nivolumab（併用）群で 55%、nivolumab 群で 56%、YERVOY 群で 39%であった。

14.2 悪性黒色種の術後補助療法

皮膚黒色腫の補助療法に用いる YERVOY の有効性は、完全切除済みのリンパ節転移陽性病変（臨床的に検出可能、又は大きさを問わず潰瘍もしくは有糸分裂が 1mm^2 以上）、in-transit 転移、サテライト転移又は転移病変を有する皮膚黒色腫患者を対象とした非盲検、多施設共同、無作為化試験である E1609 試験（NCT01274338）において評価された。登録には、無作為化前 12 週間以内の完全なリ

ンパ節廓清を伴う黒色腫の完全切除が必要であった。本試験では黒色腫の前治療歴及びステロイド治療を要する自己免疫疾患の前治療歴がある患者は不適格であった。患者は以下のレジメンのいずれかに無作為に割り付けられた：

- YERVOY 3mg/kg を 3 週間間隔で 4 回静脈内投与した後、同じ用量を 12 週間間隔で最大 4 回追加投与する
    - 高用量インターフェロンα-2b（HDI）を 2000 万単位/m^2/日の用量で週 5 日、4 週間静脈内投与（導入療法）した後、1000 万単位/m^2/日の用量で隔日、週 3 日、48 週間皮下投与（維持療法）、又は
- YERVOY 10mg/kg を 3 週間間隔で 4 回静脈内投与した後、同じ用量を 12 週間間隔で最大 4 回追加投与する

無作為化は、AJCC 第 7 版のステージ（IIIB、IIIC、M1a 又は M1b）により層別化された。腫瘍評価は、登録から 2 年は 3 ヵ月ごと、2～5 年目は 6 ヵ月ごと、5 年目以降は 12 ヵ月ごとに最長 20 年間実施された。Ipilimumab による治療は最長 60 週間、HDI による治療は最長 52 週間、又は許容できない毒性の発現、疾患進行又は同意撤回まで継続された。有効性の主要評価項目は、画像検査（CNS 病変）、画像検査及び細胞診又は組織診陽性（非 CNS 病変）に基づいた治験責任医師判定による無再発生存期間（RFS）及び全生存期間（OS）であった。YERVOY の推奨開始用量 3mg/kg の有効性の結果を以下に示す。

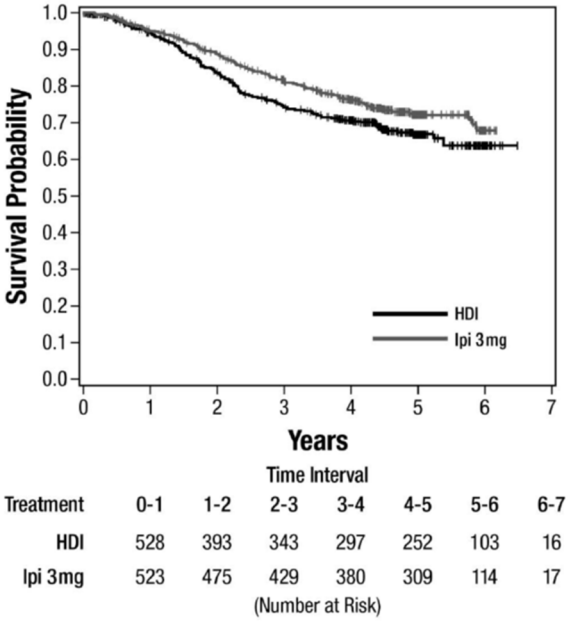
合計 1051 例の患者を YERVOY 3 mg/kg 群（523 例）及び HDI 群（528 例）に無作為に割り付けた。年齢の中央値は 54 歳（範囲：18～83）、62%が男性、97%が白人、0.3%がアジア人、0.4%が黒人であった。病期に関しては、53%が病期 IIIB、40%が病期 IIIC（in-transit 転移なし）、7%が病期 IV であった。
有効性の結果を表 27 及び図 3 に示す。

表 27：E1609 試験における有効性の結果

	YERVOY 3 mg/kg 523 例	**HDI 528 例**
全生存期間		
死亡数（%）	130 (25)	134 (25)
ハザード比（95% CI）	0.78 (0.61, 0.99)	
P 値（log-rank 検定[a]）	0.044	
5 年全生存率（95% CI）	72 (66, 76)	67 (62, 71)
無再発生存期間		
イベント数（%）	246 (47)	232 (44)
中央値（年）（95% CI）	4.5 (2.7, NA)	2.5 (1.8, 3.5)
ハザード比（95% CI）	0.85(0.71, 1.02)	

[a] 病期で層別化された。

図 3：E1609 試験における Ipilimumab 3mg/kg と HDI の全生存期間の Kaplan-Meier 曲線



14.3 進行腎細胞癌

未治療の進行性 RCC 患者を対象とした無作為化（1:1）、非盲検試験である CHECKMATE-214（NCT02231749）において、YERVOY と nivolumab の併用投与の有効性を評価した。患者は PD-L1 の発現状況によらず登録された。CHECKMATE-214 は、脳転移、活動性自己免疫性疾患、又は全身免疫抑制を要する医学的状態のいずれかの既往又は併発のある患者を除外した。患者を nivolumab 3 mg/kg と YERVOY 1 mg/kg を 3 週間ごとに 4 回静脈内投与した後、nivolumab 3 mg/kg を隔週投与する群、又はスニチニブ 50 mg/日を各 6 週間サイクルの最初の 4 週間に経口投与する群に無作為に割り付けた。疾患進行又は許容できない毒性が認められるまで投与を継続した。患者は International Metastatic RCC Database Consortium（IMDC）予後スコアおよび地域により層別化された。主要な有効性転帰指標は、Intermediate/poor リスク患者における OS、PFS（IRRC 評価）、および確定した ORR（IRRC 評価）であった。中リスク／高リスク患者には、IMDC 基準に基づく 6 つの予後危険因子［RCC の初回診断から無作為割付けまでの期間が 1 年未満、Karnofsky performance status（KPS）が 80%未満、ヘモグロビンが基準値下限未満、補正カルシウムが 10 mg/dL 超、血小板数が ULN 超、及び好中球絶対数が ULN 超］のうち 1 つ以上が認められた。

合計 847 例が無作為に割り付けられ、425 例が YERVOY と nivolumab の併用投与、422 例がスニチニブ投与に割り付けられた。年齢の中央値は 61 歳（範囲：21～85）であり、38%が 65 歳以上、8%が 75 歳以上であった。患者の大半は男性（73%）及び白人（87%）であり、ベースライン時の KPS が 70%～80%であった患者の割合は 26%、90%～100%であった患者の割合は 74%であった。

CHECKMATE-214 の有効性の結果を表 28 及び図 4 に示す。Intermediate/poor リスク患者を対象において、スニチニブと比較して、YERVOY と nivolumab との併用投与群に無作為割付された患者の OS

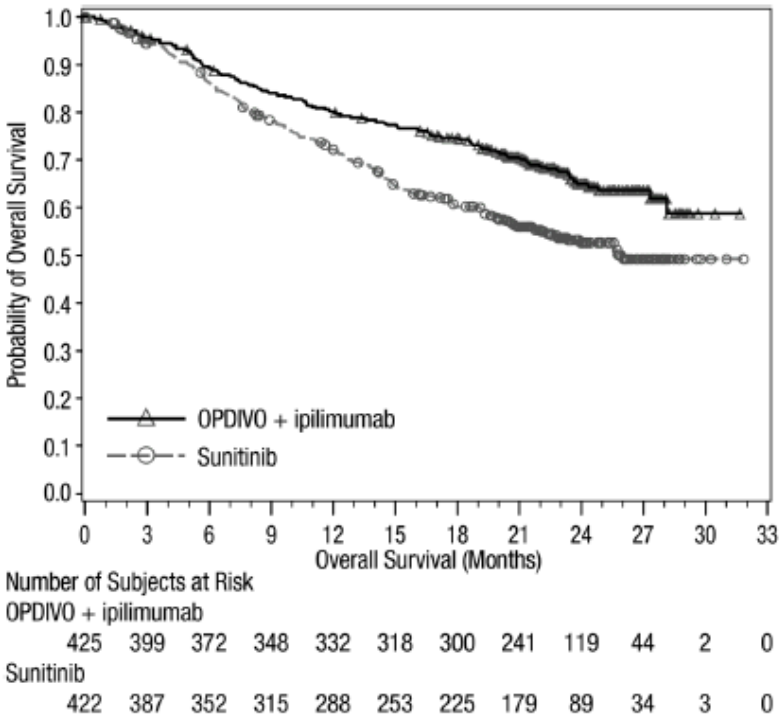
および ORR で統計的に有意な改善が示された。OS のベネフィットは PD-L1 発現レベルによらずみとめられた。試験では、PFS で統計的に有意な改善は示されなかった。

表 28：CHECKMATE-214 における有効性の結果

有効性のパラメータ	Intermediate/poor リスク	
	YERVOY 1 mg/kg と Nivolumab（n=425）	**スニチニブ（n=422）**
全生存率		
死亡数	140 (32.9%)	188 (44.5%)
生存の中央値（月）	NE	25.9
ハザード比（99.8% CI）[a]	0.63 (0.44, 0.89)	
p 値[b,c]	<0.0001	
確定した客観的奏効率（95% CI）	41.6% (36.9%, 46.5%)	26.5% (22.4%, 31.0%)
完全奏功	40 (9.4%)	5 (1.2%)
部分奏功	137 (32.2%)	107 (25.4%)
奏功した期間の中央値（月、95% CI）	NE (21.8, NE)	18.2 (14.8, NE)
p 値[d,e]	<0.0001	
無増悪生存期間		
イベント数（進行又は死亡）	228 (53.6%)	228 (54.0%)
中央値（月）	11.6	8.4
ハザード比（99.1% CI）[a]	0.82 (0.64, 1.05)	
p 値[b]	NS[f]	

[a] 層別比例ハザードモデルに基づく
[b] 層別 log-rank 検定に基づく
[c] 統計的有意性を達するための p 値は alpha 0.002 と比較される
[d] 層別 DerSimonian-Laird 法に基づく
[e] 統計的有意性を達するための p 値は alpha 0.001 と比較される
[f] alpha level 0.009 で有意ではない

図 4：CHECKMATE-214 における全生存率（Intermediate/poor リスク集団）の Kaplan-Meier 曲線



CHECKMATE-214 では、さらに、IMDC 基準の favorable リスクの患者 249 例を nivolumab と YERVOY の併用投与（n=125）又はスニチニブ（n=124）に無作為割付した。これらの患者は有効性解析集団の一部として評価されなかった。nivolumab と YERVOY を投与された favorable リスクの患者の OS では、スニチニブと比較して、ハザード比が 1.45 である（95% CI：0.75, 2.81）。Favorable リスクの未治療腎細胞癌における nivolumab と YERVOY の併用投与の有効性は確立されていない。

14.4 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の転移性結腸・直腸癌

CHECKMATE-8HW（NCT 03143153）試験は、PCR、NGS 又は IHC を用いた地域の標準的な検査法に従い、腫瘍の MSI-H 又は dMMR（MSI-H/dMMR）の状態が確認されている切除不能又は転移性 CRC を有するすべてのラインの免疫療法未治療患者を対象とした無作為化、3 群、非盲検試験であった。PCR（Idylla MSI）検査を用いた MSI-H の状態及び IHC（Omnis MMR）検査を用いた dMMR の状態の中央判定は、実施医療機関での MSI-H/dMMR の状態判定に用いた患者の腫瘍検体を用いてレトロスペクティブに実施した。いずれかお中央検査機関の検査により、MSI-H/dMMR が確認された患者を主要試験集団とした。

本試験では、症候性の脳転移を有する患者、活動性の自己免疫疾患を有する患者、全身性コルチコステロイド又は免疫抑制剤を使用している患者、又はチェックポイント阻害剤の治療歴がある患者を除外した。

患者は以下いずれかの投与群に無作為に割付けられた：

- 3 週間間隔で YERVOY 3 mg/kg と nivolumab 240 mg を最大 4 回併用投与した後、nivolumab 240 mg を 4 週間間隔で投与
- 2 週間間隔で nivolumab 240 mg を 6 回投与した後、nivolumab 480 mg を 4 週間間隔で投与
- 治験担当医師の選択した化学療法
  - ベバシズマブ又はセツキシマブのいずれかとの併用又は非併用の mFOLFOX6（オキサリプラチン、ロイコボリン及び FU）：2 週間ごとにオキサリプラチン 85 mg/m^2、ロイコボリン 400 mg/m^2 及び FU 400 mg/m^2 をボーラス投与した後、FU 2400 mg/m^2 を 46 時間かけて投与する。mFOLFOX6 投与前にベバシズマブ 5 mg/kg 又はセツキシマブ 500 mg/m^2 を 2 週間ごとに投与する。
  - ベバシズマブ又はセツキシマブのいずれかとの併用又は非併用での FOLFIRI（イリノテカン、ロイコボリン及び FU）：2 週間ごとにイリノテカン 180 mg/m^2、ロイコボリン 400 mg/m^2、並びに FU 400 mg/m^2 をボーラス投与し、FU 2400 mg/m^2 を 46 時間かけて投与する。2 週間ごとの FOLFIRI 投与前にベバシズマブ 5 mg/kg 又はセツキシマブ 500 mg/m^2 を投与する。

無作為化は、腫瘍の部位（右又は左）及び前治療ライン（0、1 又は 2L+）により層別化された。化学療法群に無作為化された患者は、BICR の評価による進行時に YERVOY と nivolumab の併用投与を受けることができた。

YERVOY と nivolumab の併用投与又は niolumab 単剤投与を受けた患者は、疾患進行又は許容できない毒性が認められるまで、又は最長 2 年間、治験薬の投与を受けた。YERVOY に起因する副作用により併用投与を中止した患者は、nivolumab 単剤投与を継続することができた。治験責任医師により臨床的ベネフィットが得られると判断され、治療に忍容性がある場合、RECIST 1.1 の評価による進行後も nivolumab を YERVOY と併用又は非併用で投与することができた。RECIST 1.1 による腫瘍評価は、最初の 24 週間は 6 週間ごと、その後 96 週目までは 8 週間ごと、その後 144 週目までは 16 週間ごと、その後は 24 週間ごとに実施された。

有効性の評価は、中央検査機関で MSI-H/dMMR であることが確認され、一次治療（1L）として YERVOY と nivolumab の併用投与に無作為化された患者と化学療法に無作為化された患者との比較、及び中央検査機関で MSI-H/dMMR であることが確認され、一次治療として YERVOY と nivolumab の併用投与に無作為化された患者と nivolumab に無作為化された患者との比較に基づいた。

主要な有効性評価項目は、RECIST 1.1 に基づく BICR 判定による PFS であった。その他の有効性評価項目は、ORR、BICR の評価による奏効期間及び OS であった。

無作為化された合計 839 例のベースライン時の特性：年齢の中央値 63 歳（範囲：20～87）で 46%が 65 歳以上、14%が 75 歳以上であった。50%が男性、87%が白人、3%がアジア人、1.5%が黒人又はアフリカ系アメリカ人、2.3%がその他の人種であった。9.2%がヒスパニック又はラテン系、41%が民族不明であった。ベースライン時の ECOG パフォーマンスステータスは 0（52%）、（48%）であった。前治療歴は 0（56%）、1（24%）、2 以上（19%）であった。腫瘍部位は患者の 69%及び 31%が右側及び左側であった。中央検査機関で MSI-H/dMMR が確認されたベースライン特性は、無作為化された全ての患者の特性と一致している。

YERVOY と nivolumab 併用の一次治療

YERVOY と nivolumab 併用投与（202 例）及び化学療法（101 例）に無作為に割り付けられた一次治療患者 303 例のうち、YERVOY と nivolumab 併用投与及び化学療法でそれぞれ 171 例及び 84 例が MSI-H/dMMR であることが確認された。

一次治療では、YERVOY と nivolumab の併用投与に割り付けられた 202 例中 200 例、化学療法に割り付けられた 101 例中 88 例が 1 回以上治験薬の投与を受けた。化学療法を受けた 88 例のうち、患者の 58%及び 42%がそれぞれオキサリプラチンを含むレジメン及びイリノテカンを含むレジメンを受け、66 例（75%）の患者がベバシズマブ（64%）又はセツキシマブ（11%）のいずれかの分子標的薬の投与を受けた。

中央判定で MSI-H/dMMR が確認され、一次治療として YERVOY と nivolumab 併用投与と化学療法に無作為に割り付けられた患者を比較した、BICR 判定による PFS の有効性の結果を表 29 および図 5 に示す。統計学的検定法により、PFS 解析時点において投与群間で ORR 及び OS を比較した結果は得られなかった。

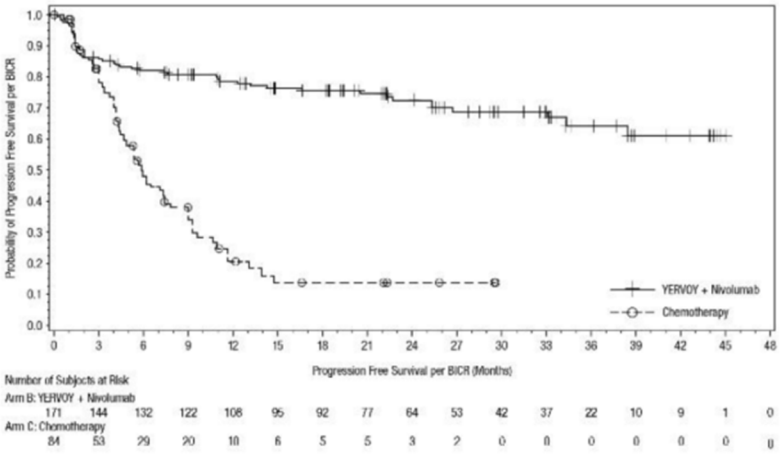
表 29：CHECKMATE-8HW における有効性の結果

	YERVOY と Nivolumab (n=171)	**化学療法 (n=84)**
無増悪生存期間		
疾患進行又は死亡（%）	48 (28)	52 (62)
中央値（月）[b]（95% CI）[a]	NR (38.4, NE)	5.8 (4.4, 7.8)
ハザード比[c]（95% CI）[a]	0.21 (0.14, 0.32)	
p 値[a]	<0.0001	

NR: 未到達、NE：推定不能
データカットオフ日の 2023 年 10 月 12 日時点で、追跡調査期間は 6.1 ヵ月以上であった。

[a] Cox 比例ハザードモデルと同じ因子で層別化した log-rank 検定に基づく。統計学的有意性の p 値の閾値は 0.0209 であった。
[b] Kaplan-Meier 法による推定値による層別 log-rank 検定に基づく。
[c] IRT による腫瘍部位（左対右）で層別化した Cox 比例ハザードモデルによる HR

図 5：CHECKMATE-8HW における無増悪期間（YERVOY と nivolumab 併用投与対化学療法）



全てのラインの YERVOY と nivolumab 併用投与

すべての治療ラインで、YERVOY と nivolumab 併用投与（354 例）及び nivolumab の単剤投与（353 例）に無作為に割り付けられた 707 例のうち、YERVOY と nivolumab 併用投与で 296 例、ニボルマブ単剤投与で 286 例が中央判定で MSI-H/dMMR であることが確認された。治験薬の投与を 1 回以上受けた患者は、OPDIVO と ipilimumab 併用投与に無作為に割り付けされた 354 例中 352 例、OPDIVO 単剤投与に無作為割り付けされた 353 例中 351 例であった。

中央判定で MSI-H/dMMR であることが確認され、YERVOY と nivolumab 併用投与に無作為化された患者と nivolumab 単剤投与を比較した、すべての治療ラインにおける BICR 評価による PFS 及び ORR の有効性の結果を表 30 及び図 6 に示す。PFS 解析時点では、統計学的検定法のため、群間の OS は得られなかった。

表 30：CHECKMATE-8HW における全ての治療ラインの有効性の結果

	YERVOY と Nivolumab (n=296)	**Nivolumab (n=286)**
無増悪生存期間		
疾患進行又は死亡（%）	101 (34)	136 (48)
中央値（月）[b] (95% CI)	NR (53.82, NE)	39.3 (22.1, NE)
ハザード比[c]（95% CI）[a]	0.62 (0.48, 0.81)	
p 値[a]	0.0003	
全体的奏効率（ORR）		
奏効率、n（%） (95% CI)	209 (71%) (65, 76)	165 (58%) (52, 63)
完全奏功率、n（%）	90 (30%)	80 (28%)
部分奏効、n（%）	119 (40%)	65 (30%)

p 値 [d]	0.0011

NR: 未到達、NE：推定不能

データカットオフ日の 2024 年 8 月 24 日時点で、追跡調査期間は 6.1 ヵ月以上であった。

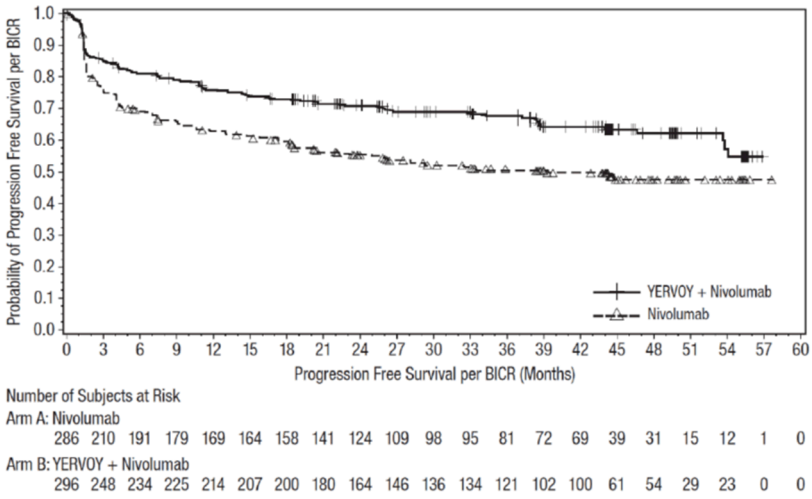
[a] Cox 比例ハザードモデルと同じ因子で層別化した log-rank 検定に基づく。統計学的有意性の p 値の閾値は 0.0095 であった。

[b] Kaplan-Meier 法による推定値に基づく

[c] 腫瘍部位（左対右）及び IRT による前治療ライン（0、1、2 以上）で層別化した Cox 比例ハザードモデルによる HR

[d] Cox 比例ハザードモデルと同じ因子で層別化した Cochran-Mantel-Haenszel 検定に基づく。統計学的有意性の p 値の閾値は 0.006 であった。

図 6：CHECKMATE-8HW における無増悪期間（全治療ライン（YERVOY と nivolumab 併用投与対 Nivolumab）



14.5 肝細胞癌

<u>切除不能又は転移性の肝細胞癌（HCC）の治療</u>

CHECKMATE-9DW（NCT04039607）は、切除不能又は転移性 HCC 成人患者（18 歳以上）を対象とした無作為化（1:1）、非盲検試験であった。患者は組織学的に確認された HCC、Child-Pugh 分類 A、ECOG パフォーマンスステータスは 0 又は 1 であり、進行性疾患に対する全身療法歴はなかった。登録前の上部消化管内視鏡検査は必須ではなかった。本試験では、活動性の自己免疫疾患、脳転移又は軟膜髄膜転移、肝性脳症の既往（無作為化前 12 ヵ月以内）、血小板数 60,000 未満、臨床的に重大な腹水、全身免疫抑制を要する疾患、HIV 感染、又は B 型肝炎ウイルス（HBV）と C 型肝炎ウイルス（HCV）もしくは HBV と D 型肝炎ウイルス（HDV）の活動性重複感染を有する患者を除外した。

患者は以下の投与群に無作為に割り付けられた：

- 3 週間間隔で YERVOY 3 mg/kg を 30 分かけて点滴静注と nivolumab 1 mg/kg を 30 分かけて点滴静注を最大 4 回併用投与した後、nivolumab 480 mg を 4 週間間隔で 30 分かけて点滴静注で単剤投与、又は
- 治験責任医師の選択により

- レンバチニブ 8 mg を 1 日 1 回経口投与（体重 60 kg 未満の場合）又は 12 mg を 1 日 1 回経口投与（体重 60 kg 以上の場合）又は
- ソラフェニブ 400 mg を 1 日 2 回経口投与

無作為化は、病因（HBV、HCV、又は非ウイルス性）、大血管浸潤及び／又は肝外進展（あり又はなし）並びにα-フェトプロテイン濃度（400 ng/mL 以上又は 400 ng/mL 未満）により層別化された。YERVOY と nivolumab の併用投与は、疾患進行又は許容できない毒性が発現するまで、又は最長 2 年間継続した。YERVOY に起因する副作用により併用療法を中止した患者は、nivolumab の単剤投与を継続することができた。患者が臨床的に安定しており、治験責任医師により臨床的ベネフィットが得られると判断された場合、RECIST v1.1 に基づく疾患進行後も投与を継続することができた。腫瘍評価は、ベースライン時、無作為化後の 9 週目及び 16 週目、その後は 48 週目までは 8 週ごと、以降は疾患進行、治験薬の投与中止又は次治療の開始まで 12 週ごとに実施した。有効性の主要評価項目は、無作為化された全被験者における OS であった。その他の有効性評価項目は、RECIST v1.1 に基づく BICR 判定による ORR 及び DOR であった。

合計 668 例の患者を YERVOY と nivolumab の併用投与（335 例）又は治験担当医師が選択したレンバチニブ又はソラフェニブ（333 例）に無作為に割り付けた。治験担当医師が選択した投与群では、患者の 85%がレンバチニブ、15%がソラフェニブの投与を受けた。試験対象集団の特性：年齢の中央値は 66 歳（範囲：20~89）で 53%が 65 歳以上、82%が男性、53%が白人、44%がアジア人、2.2%が黒人であり、ヒスパニック又はラテン系が 12%、非ヒスパニック又はラテン系が 48%、40%は報告なしであった。ベースラインの ECOG パフォーマンスステータスは 0（71%）又は 1（29%）であった。患者の 34%に HBV 感染、28%に HCV 感染が認められ、36%では HBV 又は HCV 感染のエビデンスは認められなかった。

患者の 19%がアルコール性肝疾患、11%が非アルコール性肝疾患であった。患者の大半で、ベースライン時の BCLC はステージ C（73%）であり、ステージ B が 19%、ステージ A が 6%であった。Child-Pugh スコアが 5、6 及び 7 の患者は、それぞれ 77%、20%、及び 3%であった。Child-Pugh 8 の患者が 1 例登録された。合計 54%の患者で肝外進展が認められ、25%に大血管浸潤が認められ、33%は AFP 値が 400 μg/L 以上であった。

CHECKMATE-9DW 試験において、OS 及び ORR で統計的に有意な改善が示された。最短の追跡調査期間は 26.8 ヵ月であった。有効性の結果を表 31 及び図 7 に示す。

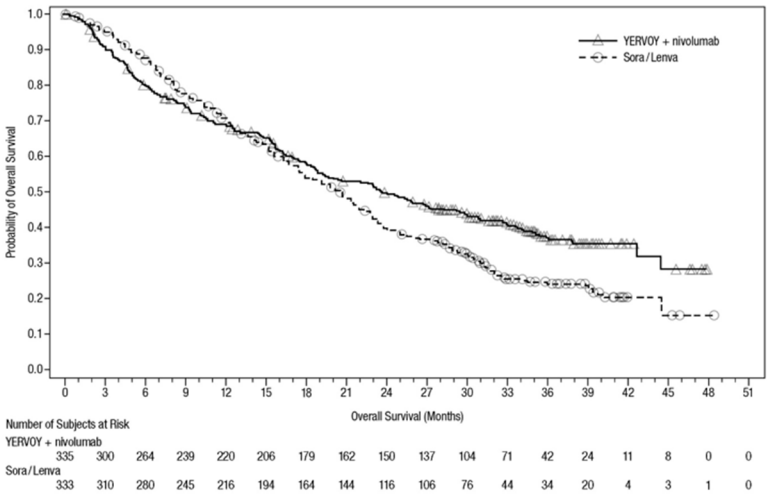
表 31：CHECKMATE-9DW における有効性の結果

	YERVOY と Nivolumab（n=335）	**レンバチニブ又はソラフェニブ（n=333）**
全生存率		
死亡数（%）	194 (58%)	228 (68%)
中央値（月）（95% CI）	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
ハザード比（95% CI）[a]	0.79 (0.65, 0.96)	
p 値[b,]	0.0180	

全奏効率, n（%）[c]	121 (36.1)	44 (13.2)
（95% CI）	(31.0, 41.5)	(9.8, 17.3)
p 値[d,]	<0.0001	
完全奏功（%）	23 (6.9)	6 (1.8)
部分奏功（%）	98 (29.3)	38 (11.4)
奏効期間（月）[c]		
中央値 （95% CI）	30.4 (21.2, NR[e])	12.9 (10.2, 31.2)
範囲	1.5+, 36.9+	2.1+, 32.5+

[a] 層別 Cox 比例ハザードモデルに基づく。
[b] 両側層別ログランク検定に基づく。統計学的優位性の境界：p 値≤0.0257
[c] RECIST v1.1 を用いた BICR による評価。
[d] 両側 Cochran-Mantel-Haenszel 検定に基づく。統計学的優位性の境界：p 値≤0.025
[e] NR：未到達
+ 打ち切り観察

図 7：CHECKMATE-9DW における全生存期間



治療歴のある肝細胞癌

CHECKMATE-040（NCT01658878）は、ソラフェニブ投与中に進行した又はソラフェニブに不耐となった HCC 患者を対象とした多施設共同、複数コホート、非盲検試験であった。その他の適格性基準は、HCC の組織学的確認及び Child-Pugh 分類 A の肝硬変であった。本試験では、活動性の自己免疫疾患、脳転移、肝性脳症の既往、臨床的に重大な腹水、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）の活動性の重複感染を有する患者を除外した。ただし、活動性の HBV 又は HCV のみを有する患者は適格とした。

CHECKMATE-040 のコホート 4 において YERVOY 3 mg/kg と nivolumab 1 mg/kg の併用投与の有効性を評価した。合計 49 例の患者に併用レジメンを投与した。併用レジメンでは、3 週ごとに 4 回投与

した後、疾患進行又は許容できない毒性が発現するまで nivolumab 240 mg を 2 週ごとに単剤投与した。

年齢の中央値は 60 歳（範囲：18～80）であった。88%が男性、74%がアジア人、25%が白人であった。ベースラインの ECOG パフォーマンスステータスは 0（61%）又は 1（39%）であった。患者の 57%に活動性 HBV 感染、8%に活動性 HCV 感染が認められたが、35%には活動性 HBV 又は HCV のエビデンスは認められなかった。HCC の病因は、患者の 16%ではアルコール性肝疾患、6%では非アルコール性肝疾患であった。Child-Pugh 分類及びスコアは A5 が 82%、A6 が 18%であった。患者の 80%に肝外転移、35%に血管浸潤が認められた。51%では α-フェトプロテイン（AFP）値が 400 µg/L 以上であった。前治療歴は手術（74%）、放射線療法（29%）又は局所療法（59%）であった。すべての患者が過去にソラフェニブの投与を受けており、このうち 10%はソラフェニブに不耐性であった。被験者の 29%が過去に 2 種類以上の全身療法を受けていた。

有効性の結果を表 32 に示す。

表 32：有効性の結果 - CHECKMATE-040 のコホート 4

	YERVOY 及び Nivolumab（コホート 4）（n=49）
BICR[a] に基づく全奏効率、n（%）、RECIST v 1.1	16 (33%)
(95% CI)[b]	(20, 48)
完全奏効	4 (8%)
部分奏効	12 (24%)
BICR[a] に基づく奏効期間、RECIST v 1.1	n=16
範囲（月）	4.6, 30.5+
奏効期間 6 ヵ月以上の割合	88%
奏効期間 12 ヵ月以上の割合	56%
奏効期間 24 ヵ月以上の割合	31%
BICR[a] に基づく全奏効率、n（%）、mRECIST	17 (35%)
(95% CI)[b]	(22, 50)
完全奏効	6 (12%)
部分奏効	11 (22%)

[a] BICR による確認。
[b] 信頼区間は Clopper-Pearson 法による。

14.6 転移性非小細胞肺癌

PD-L1 発現率 1%以上の転移性非小細胞肺癌（NSCLC）の一次治療：nivolumab との併用療法

CHECKMATE-227（NCT02477826）は転移性又は再発性 NSCLC 患者を対象とした無作為化、非盲検、複数パート試験であった。本試験には、ステージ IV 又は再発 NSCLC［7th International Association for the Study of Lung Cancer（ASLC）分類に基づく］と組織学的に確認され、ECOG パ

フォーマンスステータスが 0 又は 1 であり、過去に抗癌療法を受けたことがない 18 歳以上の患者を組み入れた。腫瘍の PD-L1 状態にかかわらず患者を組み入れた。既存の分子標的阻害剤による治療に感受性を示す EGFR 遺伝子変異又は ALK 遺伝子転座が確認されている患者、未治療の脳転移を有する患者、癌性髄膜炎患者、活動性の自己免疫疾患患者、又は全身免疫抑制療法を必要とする疾患を有する患者は本試験から除外した。脳転移の治療を受けている患者は、組入れの 2 週間以上前に神経学的にベースラインまで回復しており、コルチコステロイドを中止しているか、一定用量で継続又はプレドニゾン換算で 1 日当たり 10 mg 未満に減量している場合は適格とした。

主要な有効性の結果は、PD-L1 腫瘍発現が 1%以上の患者に限定した本試験のパート 1a に基づくものであった。中央検査機関で PD-L1 IHC 28-8 pharmDx アッセイを用いて腫瘍検体をプロスペクティブに評価した。腫瘍組織像（非扁平上皮癌又は扁平上皮癌）で層別化し無作為割付された。有効性の評価は以下の比較に基づいて行った：

- 6 週間間隔で YERVOY 1 mg/kg を 30 分かけて静脈内投与及び 2 週間間隔で nivolumab 3 mg/kg を 30 分かけて静脈内投与
- プラチナ製剤を含む 2 剤併用化学療法

化学療法は、非扁平上皮 NSCLC の場合はペメトレキセド（500 mg/m^2）とシスプラチン（75 mg/m^2）又はペメトレキセド（500 mg/m^2）とカルボプラチン（AUC 5 又は 6）の併用療法、扁平上皮 NSCLC の場合はゲムシタビン（1000 又は 1250 mg/m^2）とシスプラチン（75 mg/m^2）の併用療法又はゲムシタビン（1000 mg/m^2）とカルボプラチン（AUC 5）の併用療法（ゲムシタビンは各サイクルの Day 1 及び Day 8 に投与）とした。

治験薬の投与は、疾患進行、許容できない毒性の発現又は最長 24 ヵ月まで継続した。患者が臨床的に安定しており、治験責任医師により臨床上のベネフィットが得られていると判断された場合、疾患進行後も投与を継続した。YERVOY に起因する有害事象により併用療法を中止した患者は、nivolumab 単剤投与の継続が許可された。腫瘍評価は、最初の 12 ヵ月間は治験薬の初回投与から 6 週ごとに実施し、その後は疾患進行又は治験薬投与中止まで 12 週ごとに実施した。有効性の主要評価項目は OS とした。その他の有効性評価項目は、PFS、ORR 及び BICR の評価に基づく奏効期間とした。

パート 1a では、合計 793 例の患者を YERVOY と nivolumab の併用投与（396 例）又はプラチナ製剤を含む 2 剤併用化学療法（397 例）に無作為に割り付けた。年齢の中央値は 64 歳（範囲：26～87）であり、49%が 65 歳以上、10%が 75 歳以上、76%が白人、65%が男性であった。ベースラインの ECOG パフォーマンスステータスは 0（34%）又は 1（65%）であり、50%で PD-L1 発現率が 50%以上、組織学的に 29%が扁平上皮癌、71%が非扁平上皮癌、10%が脳転移、85%が元喫煙者／現喫煙者であった。

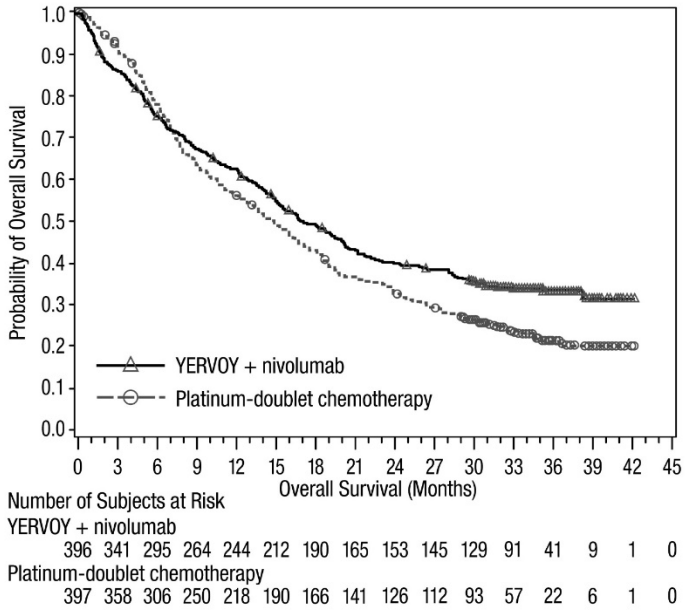
本試験では、プラチナ製剤を含む 2 剤併用化学療法群と比較して YERVOY 及び nivolumab 群に無作為化された PD-L1 発現率 1%以上の患者で OS の統計的に有意な延長が認められた。OS の結果を表 33 及び図 8 に示す。

表 33：有効性の結果（PD-L1≥1%） - CHECKMATE-227 パート 1a

	YERVOY 及び Nivolumab（n=396）	**プラチナ製剤を含む 2 剤併用化学療法（n=397）**
全生存期間		
イベント（%）	258 (65%)	298 (75%)
中央値（月）[a]（95% CI）	17.1 (15, 20.1)	14.9 (12.7, 16.7)
ハザード比（95% CI）[b]	0.79 (0.67, 0.94)	
層別ログランク検定の p 値	0.0066	

[a] Kaplan-Meier 推定値。
[b] 層別 Cox 比例ハザードモデルに基づく。

図 8：全生存期間（PD-L1≥1%）-CHECKMATE-227



BICR 評価による PFS は HR が 0.82（95% CI:0.69,0.97）であり、PFS 中央値は YERVOY と nivolumab の併用投与群で 5.1 ヵ月（95% CI:4.1,6.3）、プラチナ製剤を含む 2 剤併用化学療法群で 5.6 ヵ月（95% CI:4.6,5.8）であった。BICR 評価による確定 ORR は YERVOY 及び nivolumab 投与群で 36%（95% CI:31,41）、プラチナ製剤を含む 2 剤併用化学療法群で 30%（95% CI:26,35）であった。

YERVOY 及び nivolumab 投与群で認められた奏効期間の中央値は、プラチナ製剤を含む 2 剤併用化学療法群でそれぞれ 23.2 ヵ月及び 6.2 ヵ月であった。

転移性又は再発性 NSCLC の一次治療：nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法との併用投与

CHECKMATE-9LA（NCT03215706）は転移性又は再発性 NSCLC 患者を対象とした無作為化、非盲検試験であった。本試験には、ステージ IV 又は再発 NSCLC［7th International Association for the Study of Lung Cancer（IASLC）分類に基づく］と組織学的に確認され、ECOG パフォーマンスステータスが 0 又は 1 であり、過去に転移病変に対する抗癌療法（EGFR 阻害剤及び ALK 阻害剤を含む）を受けたことがない 18 歳以上の患者を組み入れた。腫瘍の PD-L1 状態にかかわらず患者を組み入れた。既存の分子標的阻害剤による治療に感受性を示す EGFR 遺伝子変異又は ALK 遺伝子転座が確認されている患者、未治療の脳転移を有する患者、癌性髄膜炎患者、活動性の自己免疫疾患患者又は全身免疫抑制療法を必要とする疾患を有する患者は本試験から除外した。安定した脳転移を有する患者は適格とした。

患者を以下のいずれかの群に 1:1 の比で無作為に割り付けた：

- 6 週間間隔で YERVOY 1 mg/kg を 30 分かけて静脈内投与、3 週間間隔で nivolumab 360 mg を 30 分かけて静脈内投与及び 3 週間間隔でプラチナ製剤を含む 2 剤併用化学療法を 2 サイクル静脈内投与
- 3 週間間隔でプラチナ製剤を含む 2 剤併用化学療法を 4 サイクル投与

プラチナ製剤を含む 2 剤併用化学療法は、非扁平上皮 NSCLC 患者に対してはカルボプラチン（AUC 5 又は 6）とペメトレキセド 500 mg/m^2 又はシスプラチン 75 mg/m^2 とペメトレキセド 500 mg/m^2 の併用投与のいずれか、扁平上皮 NSCLC 患者に対してはカルボプラチン（AUC 6）とパクリタキセル 200 mg/m^2 の併用投与とした。対照群の非扁平上皮 NSCLC 患者は任意でペメトレキセド維持療法を受けることができた。無作為化の層別因子は、腫瘍の PD-L1 発現率（1%以上 vs. 1%未満又は定量不能）、組織像（扁平上皮癌 vs.非扁平上皮癌）及び性別（男性 vs.女性）とした。治験薬の投与は、疾患進行、許容できない毒性の発現又は最長 2 年まで継続した。患者が臨床的に安定しており、治験責任医師により臨床上のベネフィットが得られていると判断された場合、疾患進行後も投与継続を可能とした。YERVOY に起因する副作用により併用療法を中止した患者は、本試験の一環として nivolumab 単剤投与の継続が許可された。腫瘍評価は、最初の 12 ヵ月間は治験薬の初回投与から 6 週ごとに実施し、その後は疾患進行又は治験薬投与中止まで 12 週ごとに実施した。有効性の主要評価項目は OS とした。その他の有効性評価項目は、PFS、ORR 及び BICR の評価に基づく奏効期間とした。

合計 719 例の患者を YERVOY と nivolumab の併用投与（361 例）又はプラチナ製剤を含む 2 剤併用化学療法（358 例）に無作為に割り付けた。年齢の中央値は 65 歳（範囲：26～86）であり、51%が 65 歳以上、10%が 75 歳以上であった。患者の大多数は白人（89%）及び男性（70%）であった。ベースラインの ECOG パフォーマンスステータスは 0（31%）又は 1（68%）であり、57%で PD-L1 発現率が 1%以上、37%で PD-L1 発現率が 1%未満であり、32%が扁平上皮癌の組織像、68%が非扁平上皮癌の組織像を有し、17%で CNS 転移が認められ、86%が元又は現喫煙者であった。

本試験では、OS、PFS 及び ORR に統計的に有意なベネフィットが認められた。351 件のイベントが観察された時点（最終解析の予定イベント数の 87%）で事前に規定した中間解析で得られた有効性の結果を表 34 に示す。

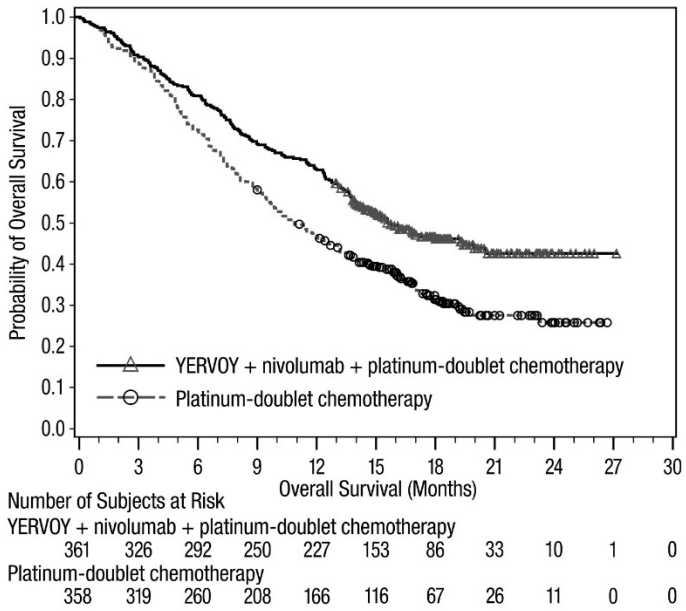
表 34：有効性の結果 - CHECKMATE-9LA

	YERVOY と Nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法（n=361）	**プラチナ製剤を含む 2 剤併用化学療法（n=358）**
全生存期間		
イベント（%）	156 (43.2)	195 (54.5)
中央値（月） （95% CI）	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
ハザード比（96.71% CI）[a]	0.69 (0.55, 0.87)	
層別ログランク検定の p 値[b]	0.0006	
BICR に基づく無増悪生存期間		
イベント（%）	232 (64.3)	249 (69.6)
ハザード比（97.48% CI）[a]	0.70 (0.57, 0.86)	
層別ログランク検定の p 値[c]	0.0001	
中央値（月）[d] （95% CI）	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
BICR に基づく全奏効率（%）	38	25
（95% CI）[e]	(33, 43)	(21, 30)
層別 CMH 検定の p 値[f]	0.0003	
BICR に基づく奏効期間		
中央値（月） （95% CI）[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

[a] 層別 Cox 比例ハザードモデルに基づく。
[b] この中間解析では、p 値を有意水準 0.033 と比較する。
[c] この中間解析では、p 値を有意水準 0.0252 と比較する。
[d] Kaplan-Meier 推定値。
[e] 信頼区間は Clopper-Pearson 法による。
[f] この中間解析では、p 値を有意水準 0.025 と比較する。

さらに 4.6 ヵ月間の追跡調査では、YERVOY と nivolumab 及びプラチナ製剤を含む 2 剤併用化学療法、又はプラチナ製剤を含む 2 剤併用化学療法を受けた患者における全生存期間のハザード比は 0.66（95% CI:0.55,0.80）、生存期間中央値はそれぞれ 15.6 ヵ月（95% CI:13.9,20.0）及び 10.9 ヵ月（95% CI:9.5,12.5）であった（図 9）。

図 9：全生存期間-CHECKMATE-9LA



14.7 悪性胸膜中皮腫

CHECKMATE-743（NCT02899299）は、切除不能な悪性胸膜中皮腫患者を対象とした無作為化、非盲検試験であった。本試験は、組織学的に確認された未治療の悪性胸膜中皮腫の患者で、治療開始前 14 日以内に緩和的放射線療法を受けていない患者を対象とした。間質性肺疾患、活動性自己免疫疾患、全身性免疫抑制を必要とする疾患又は活動性脳転移を有する患者は試験から除外した。患者を以下のいずれかに 1:1 の割合で無作為に割り付けた:

- 6 週間間隔で YERVOY 1 mg/kg を 30 分かけて静脈内投与、2 週間間隔で nivolumab 3 mg/kg を 30 分かけて静脈内投与を最長 2 年間
- 3 週間間隔でシスプラチン 75 mg/m^2 とペメトレキセド 500 mg/m^2 又はカルボプラチン AUC5 とペメトレキセド 500 mg/m^2 を 6 サイクル投与

無作為化の層別因子は腫瘍の組織型（上皮型 vs 肉腫型・二相型）及び性別（男性 vs 女性）であった。治験薬の投与は最長 2 年間、又は疾患進行もしくは許容できない毒性発現まで継続した。YERVOY に起因する副作用により併用療法を中止した患者は、nivolumab の単剤投与を継続することができた。患者が臨床的に安定しており、治験責任医師により臨床的ベネフィットが得られると判断された場合、疾患進行後も投与を継続することができた。腫瘍評価は、最初の 12 ヵ月間は治験

薬の初回投与から 6 週間ごと、その後は疾患進行又は治験薬の投与中止まで 12 週間ごとに実施した。主要有効性評価項目は OS とし、その他の有効性評価項目は PFS、ORR 及び modified RECIST 基準を用いた BICR 判定による奏効期間などとした。

合計 605 例の患者が YERVOY と nivolumab の併用投与群（303 例）と化学療法群（302 例）に無作為に割り付けられた。年齢の中央値は 69 歳（範囲：25～89）であり、72%が 65 歳以上、26%が 75 歳以上であった。85%が白人、11%がアジア人であり、77%が男性であった。ベースライン ECOG PS は 0（40%）又は 1（60%）であり、35%がステージ III、51%がステージ IV、75%が上皮型、25%が非上皮型であり、75%が PD-L1 発現が 1%以上、22%が PD-L1 発現が 1%未満であった。

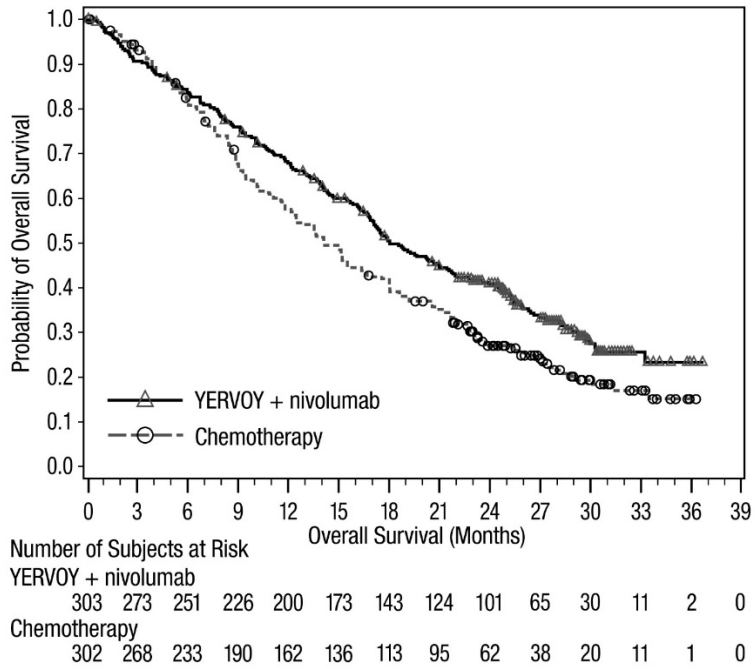
本試験では、無作為に割り付けられた YERVOY と nivolumab の併用群は、化学療法群と比較して OS に統計学的に有意な延長が認められた。事前に規定した中間解析の有効性の結果を表 35 及び図 10 に示す。

表 35: 有効性の結果- CHECKMATE-743

	YERVOY と Nivolumab (n=303)	**化学療法** (n=302)
全生存期間 [a]		
イベント(%)	200 (66)	219 (73)
中央値 (月)[b] (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
ハザード比(95% CI)[c]	0.74 (0.61, 0.89)	
層別ログランク検定の p 値 [d]	0.002	
無増悪生存期間		
イベント(%)	218 (72)	209 (69)
ハザード比(95% CI)[c]	1.0 (0.82, 1.21)	
中央値(月)[b] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
全奏効率 [e]	40%	43%
(95% CI)	(34, 45)	(37, 49)
奏効期間		
中央値(月)[a] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)

[a] 中間解析時点で 419 例が死亡（最終解析に必要な死亡の 89%）していた。
[b] Kaplan-Meier 推定値。
[c] 層別 Cox 比例ハザードモデルに基づく。
[d] この中間解析では、p 値を有意水準 0.0345 と比較する。
[e] BICR に基づく。

図 10:全生存期間- CHECKMATE-743



事前に規定した組織型別の探索的解析では、上皮型の患者部分集団における YERVOY と nivolumab の併用投与群の OS のハザード比は 0.85（95% CI:0.68, 1.06）であり、OS の中央値は YERVOY と nivolumab の併用投与群で 18.7 ヵ月、化学療法群で 16.2 ヵ月であった。非上皮型の患者部分集団におけるハザード比は 0.46（95% CI:0.31, 0.70）であり、OS の中央値は YERVOY と nivolumab の併用投与群で 16.9 ヵ月、化学療法群で 8.8 ヵ月であった。

14.8 食道癌

CHECKMATE-648（NCT03143153）は、未治療の切除不能な進行、再発又は転移性 ESCC（組織型が扁平上皮又は腺扁平上皮）患者を対象とした無作為化、実薬対照、非盲検試験であった。本試験では、中央検査機関で PD-L1 IHC 28-8 pharmDx アッセイを用いて評価した腫瘍細胞（TC）PD-L1 発現[PD-L1 腫瘍比率スコア（TPS）とも呼ばれる]が評価可能な患者を組み入れた。患者は化学放射線療法又は根治を目的とした手術に不適応であった。無作為化に使用した PD-L1 染色腫瘍検体により、複合陽性スコア（CPS）を用いて患者の腫瘍の PD-L1 の状態のレトロスペクティブな評価も実施した。根治を目的とした前治療は組み入れの 6 ヵ月以上前に終了している場合は許容された。症候性の脳転移を有する患者、活動性の自己免疫疾患を有する患者、全身性コルチコステロイド又は免疫抑制剤を使用している患者、食道腫瘍に隣接する臓器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本試験から除外した。患者は以下の投与群に無作為に割り付けられた：

- 6 週間間隔で YERVOY 1 mg/kg、2 週間間隔で nivolumab 3 mg/kg を併用投与。
- フルオロウラシル 800 mg/m^2/day を Day 1 から Day 5 まで（5 日間）静脈内投与し、シスプラチン 80 mg/m^2 を Day 1 に静脈内投与（4 週間を 1 サイクルとする）

無作為化は、PD-L1 発現率（TC）（1 以上、1 未満、又は判定不能）、地域（東アジア、その他のアジア、又は世界のその他の地域）、ECOG パフォーマンスステータス（0 又は 1）及び転移臓器数（1 以下又は 2 以上）により層別化された。主な有効性評価項目は、PD-L1 発現率（TC）が 1%以上の患者における OS 及び BICR 評価に基づく PFS であった。その他の有効性評価項目は、無作為化された全被験者における OS、無作為化された全被験者における BICR 評価に基づく PFS、PD-L1 発現率（TC）が 1%以上及び無作為化された全被験者における BICR 評価に基づく ORR であった。RECIST v.1.1 に基づく腫瘍評価は、48 週目までは 6 週間ごと、それ以降は 12 週間ごとに実施した。CHECKMATE-648 試験の A 群及び C 群に合計 649 例の患者が無作為に割り付けられ、このうち 644 例及び 601 例でそれぞれベースライン時に定量可能な PD-L1（TC）発現及び PD-L1（CPS）発現が認められ、84%（546/649 例）は PD-L1 CPS ≥1 であった。PD-L1 CPS ≥1 を有する試験対象集団の特性：年齢の中央値は 63 歳（範囲：26～81）であり、45%が 65 歳以上、84%が男性、71%がアジア人、25%が白人、1.6%が黒人又はアフリカ系アメリカ人であった。食道の扁平上皮癌（99%）又は腺扁平上皮癌（1.3%）が組織学的に確認されていた。ベースライン時の ECOG パフォーマンスステータスは 0（46%）又は 1（54%）であった。

YERVOY と nivolumab の併用療法に無作為に割り付けられた患者では、化学療法と比較して統計学的に有意な OS の改善が示された。しかし、PD-L1 CPS <1 の患者における OS の探索的解析では、HR は 1.0（95%CI 0.52, 1.94）であり、ITT 集団における改善は主に PD-L1 CPS ≥1 の患者のサブグループで観察された結果に起因することが示された。有効性の結果を表 36、図 11 及び図 12 に示す。

表 36：CHECKMATE-648 の Arm A 及び Arm C における有効性の結果

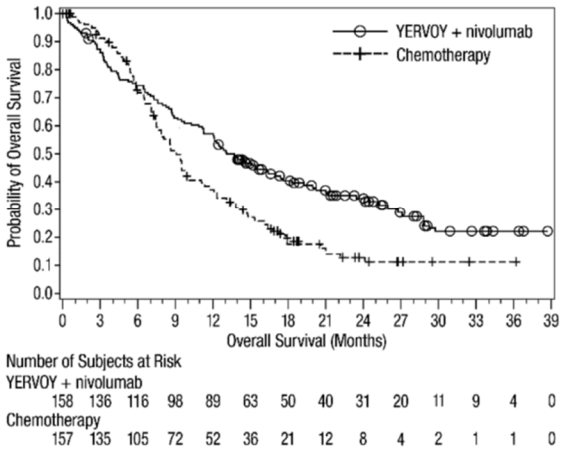
	YERVOY と Nivolumab（n=158）	**シスプラチンとフルオロウラシル（n=157）**	**YERVOY と Nivolumab（n=266）**	**シスプラチンとフルオロウラシル（n=280）**
	TC PD-L1 expression ≥1%		**PD-L1 CPS ≥1**	
全生存率				
死亡数（%）	106 (67)	121 (77)	179 (67)	205 (73)
中央値（月）（95% CI）	13.7 (11.2, 17.0)	9.1 (7.7, 10)	12.7 (10.9, 15.5)	9.8 (8.8, 11.6)
ハザード比（95% CI）[b]	0.64 (0.49, 0.84)		0.76 (0.62, 0.93)	
p 値[c]	0.0010[S1]		-	
無増悪生存期間[a]				
疾患進行又は死亡（%）	123 (78)	100 (64)	206 (77)	184 (66)
中央値（月）（95% CI）	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)	2.8 (2.6, 4.2)	5.6 (4.2, 5.9)
ハザード比（95% CI）[b]	1.02 (0.78, 1.34)		1.2 (1.0, 1.5)	
p 値[c]	NS		-	

全奏効率, n（%） [a, NT]	56 (35.4)	31 (19.7)	74 (28)	76 (27)
（95% CI）	(28.0, 43.4)	(13.8, 26.8)	(22.5, 33.6)	(22.0, 32.8)
完全奏効（%）	28 (17.7)	8 (5.1)	32 (12.0)	18 (6.4)
部分奏効（%）	28 (17.7)	23 (14.6)	42 (15.8)	58 (20.7)
中央値 （95% CI）	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)	11.8 (7.1, 23.6)	6.9 (5.7, 8.2)
範囲	1.4+, 34.5+	1.4+, 31.8+	1.4+, 34.5+	1.4+, 31.8+

[a] BICR に基づく。
[b] 層別 Cox 比例ハザードモデルに基づく。ハザード比は各解析対象集団内で化学療法と比較した nivolumab を含む各群について報告された。
[c] 層別両側ログランク検定に基づく。
[S1] 0.014 の中止境界と比較して有意な p 値。
NS：統計学的に有意ではない、NT：事前に規定した階層的検定手順に従い、統計学的優位性を評価しなかった。

図 11:全生存期間 - CHECKMATE-648

(A) TC PD-L1 ≥1%の全生存期間



(B) PD-L1 CPS ≥1 の全生存期間

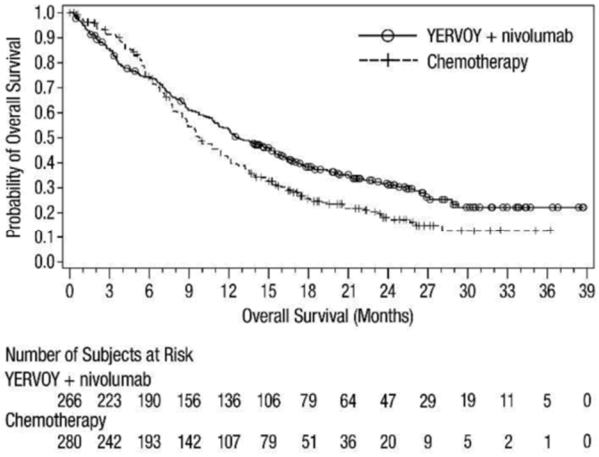
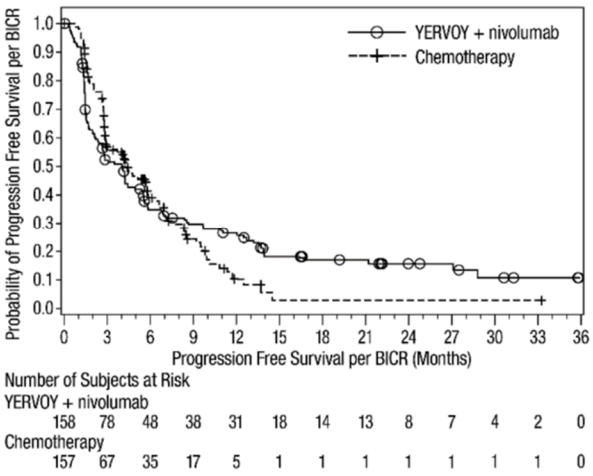
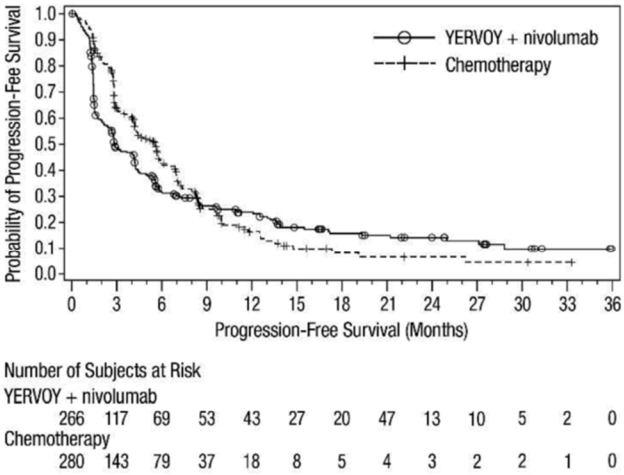


図 12:無増悪生存期間- CHECKMATE-648

(A) TC PD-L1 ≥1%の無増悪存期間



(B) PD-L1 CPS ≥1 の無増悪生存期間



ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 5 mg ipilimumab.
One 10 ml vial contains 50 mg of ipilimumab.
One 40 ml vial contains 200 mg of ipilimumab.

Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody (IgG1κ) produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipients with known effect:

Each ml of concentrate contains 0.1 mmol sodium, which is 2.30 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates and has a pH of 7.0 and an osmolarity of 260-300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

YERVOY as monotherapy or in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older (see section 4.4).

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).

Renal cell carcinoma (RCC)

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see section 5.1).

Non-small cell lung cancer (NSCLC)

YERVOY in combination with nivolumab 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.

Malignant pleural mesothelioma (MPM)

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

YERVOY in combination with nivolumab 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)

YERVOY in combination with nivolumab 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%.

Hepatocellular carcinoma (HCC)

YERVOY in combination with nivolumab 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 specialist physicians experienced in the treatment of cancer.

PD-L1 testing

If specified in the indication, patient selection for treatment with YERVOY based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, and 5.1).

MSI/MMR testing
If specified in the indication, patient selection for treatment with YERVOY 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

YERVOY as monotherapy

Melanoma
Adults and adolescents 12 years of age and older
The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously over a 30-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.

YERVOY in combination with nivolumab

Melanoma
In adults and adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab 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 1. 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 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab 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 1. 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 1: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab

	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 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	-

Renal cell carcinoma

The recommended dose is 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab 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 2. For the monotherapy phase, the first dose of nivolumab should be administered;

- 3 weeks after the last dose of the combination of ipilimumab and nivolumab if using 240 mg every 2 weeks; or
- 6 weeks after the last dose of the combination of ipilimumab and nivolumab if using 480 mg every 4 weeks.

Table 2: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab 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 1 mg/kg ipilimumab in combination with 240 mg of nivolumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by 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. 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 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab 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 3. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of ipilimumab and nivolumab.

Table 3: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab 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	-

Malignant pleural mesothelioma

The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks. Treatment is continued for up to 24 months in patients without disease progression.

Oesophageal squamous cell carcinoma

The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30 minutes. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Hepatocellular carcinoma

The recommended dose is 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab 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 4. 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 4: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab 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	-

YERVOY in combination with nivolumab and chemotherapy

Non-small cell lung cancer
The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 1 mg/kg ipilimumab every 6 weeks in combination with 360 mg nivolumab administered intravenously every 3 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Duration of treatment
Treatment with YERVOY in combination with nivolumab, 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).

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 YERVOY in combination with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Tables 5A, 5B, and section 4.4).

Children younger than 12 years of age
The safety and efficacy of ipilimumab in children younger than 12 years of age has not been established.

Permanent discontinuation of treatment or withholding of doses

Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see section 4.4).

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Guidelines for permanent discontinuation or withholding of doses are described in Tables 5A and 5B for YERVOY as monotherapy, and in Table 5C for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 5A: When to permanently discontinue YERVOY as monotherapy

Permanently discontinue YERVOY in patients with the following adverse reactions. Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related (see section 4.4 for detailed management guidelines).	
Adverse reactions	**NCI-CTCAE v4 Grade[a]**
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	▪ Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	▪ Grade 3 or 4 elevation in AST, ALT, or total bilirubin
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, diabetes)	▪ ≥ Grade 3 immune-related reactions[c] ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy ▪ Grade 4 diabetes

[a] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI-CTCAE v4).

[b] Any other adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to discontinue YERVOY should be based on severity.

[c] Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

Table 5B: When to withhold dose of YERVOY as monotherapy

Withhold YERVOY dose[a] in patients with the following immune-related adverse reactions. See section 4.4 for detailed management guidelines.	
Adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs, resume therapy.[d] 3. If resolution has not occurred, continue to withhold doses until resolution then resume treatment.[d] 4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Grade 2 elevation in AST, ALT, or total bilirubin	
Skin: Moderate to severe (Grade 3)[b] skin rash or (Grade 2) widespread/intense pruritus regardless of etiology	
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy Grade 3 diabetes	

Withhold YERVOY dose[a] in patients with the following immune-related adverse reactions. See section 4.4 for detailed management guidelines.	
Adverse reactions	**Action**
Neurological: Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse reactions[c]	

[a] No dose reduction of YERVOY is recommended.

[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI-CTCAE v4).

[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. Decision whether to withhold a dose should be based on severity.

[d] Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

Table 5C: Recommended treatment modifications for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment

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 or 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis without HCC	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 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 adverse reaction	Severity	Treatment modification
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[a] 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[b]
	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] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

[b] The safety of re-initiating ipilimumab in combination with nivolumab therapy in patients previously experiencing immune-related myocarditis is not known.

YERVOY in combination with nivolumab should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

When YERVOY is administered in combination with nivolumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient.

Special populations

Paediatric population

The safety and efficacy of YERVOY as monotherapy in children younger than 12 years of age have not been established. Very limited data are available. YERVOY should not be used in children younger than 12 years of age.

The safety and efficacy of YERVOY in combination with nivolumab in children younger than 18 years of age have not been established, except in adolescents 12 years of age and older with melanoma. Currently available data are described in sections 4.2, 4.8, 5.1 and 5.2.

Elderly
No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from first-line RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). No specific dose adjustment is necessary in this population (see section 5.1).

Renal impairment
The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see section 5.2).

Hepatic impairment
The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild hepatic impairment (see section 5.2). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see section 5.1).

Method of administration

YERVOY is for intravenous use. The recommended infusion period is 30 minutes.

YERVOY can be used for intravenous administration without dilution or may be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection to concentrations between 1 and 4 mg/ml.

YERVOY must not be administered as an intravenous push or bolus injection.

When administered in combination with nivolumab or in combination with nivolumab and chemotherapy, nivolumab should be given first followed by YERVOY and then by chemotherapy (if applicable) 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.

Ipilimumab in combination with nivolumab

When ipilimumab is administered in combination, refer to the Summary of Product Characteristics of the other combination therapy components prior to initiation of treatment. For additional information on warnings and precautions associated with nivolumab treatment, please refer to the nivolumab SmPC. 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 have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy.

Cardiac and pulmonary adverse events 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. Ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab may occur at any time during or after discontinuation of therapy.

Immune-related reactions

Ipilimumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions occurred during the induction period, onset months after the last dose of ipilimumab has also been reported. Unless an alternate etiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.
Ipilimumab specific management guidelines for immune-related adverse reactions are described below for use as monotherapy and in combination with nivolumab.

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, ipilimumab, or ipilimumab in combination with nivolumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction that occurs as a consequence of combination therapy, 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.

Ipilimumab in combination with nivolumab 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.

Ipilimumab in combination with nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Immune-related gastrointestinal reactions

Ipilimumab as monotherapy
Ipilimumab is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in clinical trials (see section 4.8).

In patients who received ipilimumab 3 mg/kg monotherapy in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1), the median time to onset of severe or fatal (Grade 3-5) immune-related gastrointestinal reactions was 8 weeks (range 5 to 13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution (defined as improvement to mild [Grade 1] or less or to the severity at baseline) occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks). Patients must be monitored for gastrointestinal signs and symptoms that may be indicative of immune-related colitis or gastrointestinal perforation. Clinical presentation may include diarrhoea, increased frequency of bowel movements, abdominal pain, or haematochezia, with or without fever. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration. Post-marketing cases of cytomegalovirus (CMV) infection/reactivation have been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate etiologies.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per NCI-CTCAE v4 severity grading classification). Patients with mild to moderate (Grade 1 or 2) diarrhoea (an increase of up to 6 stools per day) or suspected mild to moderate colitis (e.g. abdominal pain or blood in stools) may remain on ipilimumab. Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of ipilimumab should be withheld and corticosteroid therapy (e.g. prednisone 1 mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, ipilimumab may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see section 4.2), and systemic high-dose intravenous corticosteroid therapy should be initiated immediately. (In clinical trials, methylprednisolone 2 mg/kg/day has been used). Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment. In clinical trials, rapid tapering (over periods < 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.

The experience from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis is limited. Addition of an alternative immunosuppressive agent to the corticosteroid regimen should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including Cytomegalovirus (CMV) infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial and parasitic etiology). In clinical trials, a single dose of infliximab 5 mg/kg was added unless contraindicated. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected (see the Summary of Product Characteristics for infliximab).

Immune-related colitis

Ipilimumab in combination with nivolumab
Severe diarrhoea or colitis has been observed with ipilimumab in combination with nivolumab (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. Infectious and disease-related aetiologies should be ruled out.

For Grade 4 diarrhoea or colitis, ipilimumab in combination with nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Grade 3 diarrhoea or colitis observed with ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related pneumonitis

Ipilimumab in combination with nivolumab
Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with ipilimumab in combination with nivolumab (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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related hepatotoxicity

Ipilimumab as monotherapy
Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials (see section 4.8).

In patients who received ipilimumab 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to severe or fatal (Grade 2-5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. With protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks.

Hepatic transaminase and bilirubin must be evaluated before each dose of ipilimumab, as early laboratory changes may be indicative of emerging immune-related hepatitis (see section 4.2). Elevations in LFTs may develop in the absence of clinical symptoms. Increases in AST and ALT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, tumour progression, or concomitant medication and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

For patients with Grade 2 transaminase or total bilirubin elevation, the scheduled dose of ipilimumab should be withheld, and LFTs must be monitored until resolution. Upon improvement, ipilimumab may be resumed (see section 4.2).

For patients with Grade 3 or 4 transaminase or total bilirubin elevation, treatment must be permanently discontinued (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g.

methylprednisolone 2 mg/kg daily or equivalent) should be initiated immediately. In such patients, LFTs must be monitored until normalization. Once symptoms have resolved and LFTs show sustained improvement or return to baseline, the initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.

For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, mycophenolate mofetil was used in patients without response to corticosteroid therapy, or who had an LFT elevation during corticosteroid tapering that was not responsive to an increase in the dose of corticosteroids (see the Summary of Product Characteristics for mycophenolate mofetil).

Ipilimumab in combination with nivolumab
Severe hepatitis has been observed with ipilimumab in combination with nivolumab (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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related skin adverse reactions

Caution should be used when considering the use of ipilimumab or ipilimumab in combination with nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy).

Ipilimumab as monotherapy
Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Rare cases of toxic epidermal necrolysis (TEN) (including Steven Johnson Syndrome) have been observed, some with fatal outcome. Rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported in clinical trials and during post-marketing use (see section 4.8).

DRESS presents as a rash with eosinophilia associated with one or more of the following features: fever, lymphadenopathy, facial oedema, and internal organ involvement (hepatic, renal, pulmonary). DRESS may be characterised by a long latency (two to eight weeks) between medicinal product exposure and disease onset.

Ipilimumab-induced rash and pruritus were predominantly mild or moderate (Grade 1 or 2) and responsive to symptomatic therapy. In patients who received ipilimumab 3 mg/kg monotherapy in MDX010-20, the median time to onset of moderate to severe or fatal (Grade 2-5) skin adverse reactions was 3 weeks (range 0.9-16 weeks) from start of treatment. With protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

Ipilimumab-induced rash and pruritus should be managed based on severity. Patients with a mild to moderate (Grade 1 or 2) rash may remain on ipilimumab therapy with symptomatic treatment (e.g. antihistamines). For mild to moderate rash or mild pruritus that persists for 1 to 2 weeks and does not

improve with topical corticosteroids, oral corticosteroid therapy should be initiated (e.g. prednisone 1 mg/kg once daily or equivalent).

For patients with a severe (Grade 3) rash, the scheduled dose of ipilimumab should be withheld. If initial symptoms improve to mild (Grade 1) or resolve, ipilimumab therapy may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with a very severe (Grade 4) rash or severe (Grade 3) pruritus (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled, initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

Ipilimumab in combination with nivolumab
Severe rash has been observed with ipilimumab in combination with nivolumab (see section 4.8). Ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab, permanent discontinuation of treatment is recommended (see section 4.2).

Immune-related neurological reactions

Ipilimumab as monotherapy
Ipilimumab is associated with serious immune-related neurological adverse reactions. Fatal Guillain-Barré syndrome has been reported in clinical trials. Myasthenia gravis-like symptoms have also been reported (see section 4.8). Patients may present with muscle weakness. Sensory neuropathy may also occur.

Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting > 4 days must be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic syndromes and concomitant medication should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to ipilimumab, the scheduled dose should be withheld. If neurologic symptoms resolve to baseline, the patient may resume ipilimumab (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to ipilimumab (see section 4.2). Patients must be treated according to institutional guidelines for management of sensory neuropathy, and intravenous corticosteroids (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately.

Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality (see section 4.2).

Immune-related nephritis and renal dysfunction

Ipilimumab in combination with nivolumab
Severe nephritis and renal dysfunction have been observed with ipilimumab in combination with nivolumab (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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related endocrinopathy

Ipilimumab as monotherapy
Ipilimumab can cause inflammation of the endocrine system organs, manifesting as hypophysitis, hypopituitarism, adrenal insufficiency, hypothyroidism, Type 1 diabetes mellitus and diabetic ketoacidosis (see sections 4.2 and 4.8), and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioural changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms must be excluded. Clinical experience with ipilimumab associated endocrinopathy is limited.

For patients who received ipilimumab 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to very severe (Grade 2-4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with immunosuppressive therapy and hormone replacement therapy.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for presence of sepsis or infections. If there are signs of adrenal insufficiency but the patient is not in adrenal crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy (e.g. dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of ipilimumab should be withheld (see section 4.2). It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

For symptomatic diabetes, 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. Ipilimumab must be permanently discontinued for life-threatening diabetes.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with ipilimumab may be resumed and initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

Ipilimumab in combination with nivolumab
Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with ipilimumab in combination with nivolumab (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, ipilimumab in combination with nivolumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Ipilimumab in combination with nivolumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, ipilimumab in combination with nivolumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab may be resumed after corticosteroid taper, if needed. Ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Ipilimumab in combination with nivolumab must be permanently discontinued for life-threatening diabetes.

Infusion reaction

Ipilimumab as monotherapy or in combination with nivolumab
Severe infusion reactions have been reported in clinical trials of ipilimumab or ipilimumab in combination with nivolumab (see section 4.8). In case of a severe or life-threatening infusion reaction, the ipilimumab or ipilimumab in combination with nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab or ipilimumab in combination with nivolumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Other immune-related adverse reactions

Ipilimumab as monotherapy
The following adverse reactions suspected to be immune-related have been reported in patients treated with ipilimumab 3 mg/kg monotherapy in MDX010-20: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with ipilimumab 3 mg/kg + gp100 peptide vaccine in MDX010-20. Cases of Vogt-Koyanagi-Harada syndrome, serous retinal detachment, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8).

If severe (Grade 3 or 4), these reactions may require immediate systemic high-dose corticosteroid therapy and discontinuation of ipilimumab (see section 4.2). For ipilimumab-related uveitis, iritis,

serous retinal detachment or episcleritis, topical corticosteroid eye drops should be considered as medically indicated. Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with ipilimumab. Treatment with ipilimumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with ipilimumab versus the risk of possible organ rejection should be considered in these patients.

Ipilimumab as monotherapy or in combination with a PD-1 or PD-L1 inhibitor
Haemophagocytic lymphohistiocytosis (HLH) has been observed with ipilimumab as monotherapy and ipilimumab in combination with a PD-1 or PD-L1 inhibitor (including with nivolumab). Caution should be taken when ipilimumab is administered as monotherapy or in combination with a PD-1 or PD-L1 inhibitor. If HLH is confirmed, administration of ipilimumab or ipilimumab in combination with a PD-1 or PD-L1 inhibitor should be discontinued and treatment for HLH initiated.

Ipilimumab in combination with nivolumab
The following immune-related adverse reactions were reported in less than 1% of patients treated with ipilimumab in combination with nivolumab 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, serous retinal detachment, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8). Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.

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, ipilimumab in combination with nivolumab should be withheld and corticosteroids administered. Upon improvement, ipilimumab in combination with nivolumab may be resumed after corticosteroid taper. Ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab. 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, ipilimumab in combination with nivolumab 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, ipilimumab in combination with nivolumab should be withheld or permanently discontinued (see section 4.2).

<u>Disease specific precautions</u>

Melanoma
Patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the MDX010-20 trial (see section 5.1).

Patients with ocular melanoma were not included in the CA184-169 clinical trial. However, patients with brain metastases were included in this study, if they were free of neurologic symptoms related to metastatic brain lesions and if they did not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy (see section 5.1).

Patients with ocular melanoma, active brain metastases and prior therapy with ipilimumab were not included in the paediatric trial CA184070 (see section 5.1).

Patients with ocular melanoma, active brain metastases and prior therapy with CTLA-4, PD-1, PD-L1, or CD137 targeted agents were not included in the paediatric trial CA184178 (see section 5.1).

Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of ipilimumab in combination with nivolumab. Patients with ocular/uveal melanoma were excluded from clinical trials of melanoma. 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.

Relative to nivolumab monotherapy, an increase in PFS for the combination of ipilimumab with nivolumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between ipilimumab with nivolumab 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 ipilimumab in combination with nivolumab in melanoma patients with rapidly progressing disease.
Physicians should consider the delayed onset of ipilimumab in combination with nivolumab effect before initiating treatment in patients with rapidly progressing disease (see section 5.1).

Renal cell carcinoma
Patients with any history of concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of ipilimumab in combination with nivolumab (see sections 4.5 and 5.1). In the absence of data, ipilimumab in combination with 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
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, ipilimumab in combination with nivolumab and chemotherapy should be used with caution 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, ipilimumab in combination with 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, ipilimumab in combination with nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Oesophageal squamous cell carcinoma
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, ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab compared to chemotherapy. Physicians should consider the delayed onset of effect of ipilimumab in combination with nivolumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease (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 randomization), 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, ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab in patients with poor prognostic features.

Patients with autoimmune disease

Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism), including those who require systemic immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance, were not evaluated in clinical trials. Ipilimumab is a T-cell potentiator that enables the immune response (see section 5.1) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In other patients with a history of autoimmune disease, ipilimumab should be used with caution after careful consideration of the potential risk-benefit on an individual basis.

Patients on controlled sodium diet

This medicinal product contains 23 mg sodium per 10 ml vial and 92 mg sodium per 40 ml vial, respectively equivalent to 1.15% and 4.60% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration when treating patients on a controlled sodium diet.

Concurrent administration with vemurafenib

In a Phase 1 trial, asymptomatic grade 3 increases in transaminases (ALT/AST > 5 × ULN) and bilirubin (total bilirubin > 3 × ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and vemurafenib is not recommended.

Sequential administration with vemurafenib

In a Phase 2 trial, the sequential treatment with vemurafenib followed by 10 mg/kg ipilimumab in patients with BRAF-mutated metastatic melanoma showed a higher incidence of Grade 3+ skin adverse reactions than with ipilimumab alone. Caution should be used when ipilimumab is administered following prior vemurafenib.

Paediatric population

Limited, but no long-term, safety data is available on the use of ipilimumab in adolescents 12 years of age and older.

Only very limited data are available in children younger than 12 years of age. Therefore, ipilimumab should not be used in children younger than 12 years of age.

Before initiating treatment with ipilimumab monotherapy in adolescents of 12 years and older, physicians are advised to carefully evaluate the individual patient, taking into consideration the limited available data, the observed benefits and the toxicity of ipilimumab monotherapy in the paediatric population (see sections 4.8 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Ipilimumab is a human monoclonal antibody that is not metabolised by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes.

A drug-interaction study in adults of ipilimumab administered alone and in combination with chemotherapy (dacarbazine or paclitaxel/carboplatin) was conducted evaluating interaction with CYP isozymes (particularly CYP1A2, CYP2E1, CYP2C8, and CYP3A4) in patients with treatment-naive advanced melanoma. No clinically relevant pharmacokinetic drug-drug interaction was observed between ipilimumab and paclitaxel/carboplatin, dacarbazine or its metabolite, 5-aminoimidazole-4-carboxamide (AIC).

Other forms of interaction

Corticosteroids
The use of systemic corticosteroids at baseline, before starting ipilimumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting ipilimumab treatment does not appear to impair the efficacy of ipilimumab.

Anticoagulants
The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab (see section 4.8), patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of ipilimumab in pregnant women. Animal reproduction studies have shown reproductive toxicity (see section 5.3). Human IgG1 crosses the placental barrier. The potential risk of treatment to the developing foetus is unknown. YERVOY is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

Breast-feeding

Ipilimumab has been shown to be present at very low levels in milk from cynomolgus monkeys treated during pregnancy. It is unknown whether ipilimumab is secreted in human milk. Secretion of IgGs in human milk is generally limited and IgGs have a low oral bioavailability. Significant systemic exposure of the infant is not expected and no effects on the breast-fed newborn/infant are anticipated. However, because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue from YERVOY therapy taking into account the benefit of breast-feeding for the child and the benefit of YERVOY therapy for the woman.

Fertility

Studies to evaluate the effect of ipilimumab on fertility have not been performed. Thus, the effect of ipilimumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

YERVOY has 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 ipilimumab does not adversely affect them.

4.8 Undesirable effects

Ipilimumab as monotherapy (see section 4.2)

a. Summary of safety profile

Ipilimumab has been administered to approximately 10 000 patients in a clinical programme evaluating its use with various doses and tumour types. Unless otherwise specified, the data below reflect exposure to ipilimumab at 3 mg/kg in clinical trials of melanoma. In the Phase 3 study MDX010-20, (see section 5.1), patients received a median of 4 doses (range 1-4).

Ipilimumab is most commonly associated with adverse reactions resulting from increased or excessive immune activity. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of ipilimumab (see section 4.4 for management of immune-related adverse reactions).

In patients who received 3 mg/kg ipilimumab monotherapy in MDX010-20, the most frequently reported adverse reactions (≥ 10% of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority were mild to moderate (Grade 1 or 2). *Ipilimumab* therapy was discontinued for adverse reactions in 10% of patients.

b. Tabulated list of adverse reactions

Adverse reactions reported in patients with advanced melanoma who were treated with ipilimumab 3 mg/kg in clinical trials (n = 767) and from post-marketing surveillance are presented in Table 6.

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. Rates of immune-related adverse reactions in HLA-A2*0201 positive patients who received ipilimumab in MDX010-20 were similar to those observed in the overall clinical programme.

The safety profile of ipilimumab 3 mg/kg in chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials (N = 75; treated), in treatment-naive patients in two retrospective observational studies (N = 273 and N = 157), and in CA184-169 (N = 362) was similar to that in previously-treated advanced melanoma.

The safety data for patients with unresectable or metastatic melanoma, treated with ipilimumab (3 mg/kg, with a minimum of 3 year follow-up) and enrolled in multi-national, prospective, observational study CA184143 (N = 1151) were similar to what has been reported in ipilimumab clinical trials for advanced melanoma.

Table 6: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg[a]

Infections and infestations	
Common	sepsis[b], urinary tract infection, respiratory tract infection
Uncommon	septic shock[b], pneumonia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopaenia, thrombocytopaenia, neutropaenia
Uncommon	haemolytic anaemia[b], eosinophilia
Not known	haemophagocytic lymphohistiocytosis[e]
Immune system disorders	
Uncommon	hypersensitivity
Very rare	anaphylactic reaction
Not known	solid organ transplant rejection[e]
Endocrine disorders	
Common	hypopituitarism (including hypophysitis)[c], hypothyroidism[c]
Uncommon	adrenal insufficiency[c], secondary adrenocortical insufficiency[d], hyperthyroidism[c], hypogonadism
Rare	autoimmune thyroiditis[d], thyroiditis[d]
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalaemia, weight decreased, hyponatremia
Uncommon	alkalosis, hypophosphatemia, tumour lysis syndrome, hypocalcaemia[d]
Rare	type 1 diabetes mellitus (including diabetic ketoacidosis)[h]
Psychiatric disorders	
Common	confusional state, depression
Uncommon	mental status changes, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy, cranial neuropathy, brain oedema, peripheral neuropathy
Uncommon	Guillain-Barré syndrome[b,c], meningitis (aseptic), autoimmune central neuropathy (encephalitis)[d], syncope, ataxia, tremor, myoclonus, dysarthria
Rare	myasthenia gravis[d]
Not known	myelitis

Eye disorders	
Common	blurred vision, eye pain
Uncommon	uveitis[c], vitreous haemorrhage, iritis[c], eye oedema[d], blepharitis[d], reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Rare	Vogt-Koyanagi-Harada syndrome[e], serous retinal detachment
Cardiac disorders	
Common	arrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy[b], peripheral ischaemia, orthostatic hypotension
Rare	temporal arteritis[d]
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, cough, allergic rhinitis
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis
Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea, constipation, abdominal pain
Common	gastrointestinal haemorrhage, colitis[b,c], gastroesophageal reflux disease, mucosal inflammation[d], gastroenteritis, stomatitis
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c], peritonitis[b], diverticulitis, pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus[d], proctitis[d]
Rare	pancreatic exocrine insufficiency; coeliac disease
Hepatobiliary disorders	
Common	abnormal hepatic function
Uncommon	hepatic failure[b,c], hepatitis, hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus[c]
Common	dermatitis, erythema, vitiligo, urticaria, eczema[d], alopecia, night sweats, dry skin
Uncommon	toxic epidermal necrolysis[b,c], leukocytoclastic vasculitis, skin exfoliation, hair colour changes[d]
Rare	erythema multiforme[d], psoriasis[d], Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)[d]
Not known	pemphigoid
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[f]
Common	arthralgia, myalgia, muscle spasms, arthritis
Uncommon	polymyalgia rheumatica, myositis[d], muscular weakness[d]
Rare	polymyositis[d]
Renal and urinary disorders	
Common	renal failure[b]
Uncommon	glomerulonephritis[c], autoimmune nephritis[d], renal tubular acidosis, haematuria[d], cystitis noninfective[g], proteinuria[d]
Reproductive system and breast disorders	
Uncommon	amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia, oedema, pain
Common	chills, asthenia, influenza-like illness[d]
Uncommon	multi-organ failure[b,c], systemic inflammatory response syndrome[d], infusion related reaction

Investigations	
Common	increased alanine aminotransferase[c], increased aspartate aminotransferase[c], increased blood alkaline phosphatase[d], increased blood bilirubin, increased lipase[c],
Uncommon	increased gamma-glutamyltransferase[d], increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, increased blood amylase[c], positive antinuclear antibody[d], decreased blood testosterone
Rare	decreased blood thyroid stimulating hormone[d], decreased thyroxine[d], abnormal blood prolactin[d]

Adverse reaction frequencies presented in Table 6 may not be fully attributable to ipilimumab, but may contain contributions from the underlying disease.

[a] Frequencies are based on pooled data from 9 clinical trials investigating the ipilimumab 3 mg/kg dose in melanoma.
[b] Including fatal outcome.
[c] Additional information about these potentially inflammatory adverse reactions is provided in "Description of selected adverse reactions" and section 4.4. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.
[d] Data outside the 9 completed clinical trials in melanoma were included in frequency determinations.
[e] Post-marketing event (also see section 4.4).
[f] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
[g] Reported in clinical studies and in the post-marketing setting.
[h] Type 1 diabetes mellitus that may be associated with diabetic ketoacidosis

Additional adverse reactions not listed in Table 6 have been reported in patients who received other doses (either < or > 3 mg/kg) of ipilimumab in clinical trials of melanoma. These additional reactions occurred at a frequency of < 1% unless otherwise noted: meningism, myocarditis, pericardial effusion, cardiomyopathy, autoimmune hepatitis, erythema nodosum, autoimmune pancreatitis, hyperpituitarism, hypoparathyroidism, infectious peritonitis, episcleritis, scleritis, Raynaud's phenomenon, palmar-plantar erythrodysaesthesia syndrome, cytokine release syndrome, sarcoidosis, decreased blood gonadotrophin, leukopenia, polycythaemia, lymphocytosis, ocular myositis, and neurosensory hypoacusis.

The overall safety profile of ipilimumab 3 mg/kg in clinical trial CA184-169 (N = 362) was consistent with that established for ipilimumab in patients treated for advanced melanoma.

Ipilimumab in combination with nivolumab (with or without chemotherapy) (see section 4.2)

a. Summary of the safety profile

When ipilimumab is administered in combination, refer to the SmPC for the other therapeutic agent(s) prior to initiation of treatment. For additional information on the safety profile of the other therapeutic agents used in combination with ipilimumab, please refer to the respective SmPC.

In the pooled dataset of ipilimumab administered in combination with nivolumab (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 ipilimumab in combination with nivolumab (with or without chemotherapy), with 1.0% fatal adverse reactions attributed to study drug. Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 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 ipilimumab in combination with nivolumab (with or without chemotherapy) incidence rate. Among patients treated with ipilimumab 1 mg/kg in combination with nivolumab 360 mg 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 ipilimumab in combination with nivolumab (with or without chemotherapy) incidence rate.

b. Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with ipilimumab in combination with nivolumab (with or without chemotherapy) (n = 2626) and from post-marketing are presented in Table 7. 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 7: Adverse reactions with ipilimumab in combination with other therapeutic agents

	Combination with nivolumab (with or without chemotherapy)
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis
Rare	aseptic meningitis
Blood and lymphatic system disorders	
Very common	anaemia[b,i], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]
Common	eosinophilia
Uncommon	febrile neutropaenia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	infusion-related reaction (including cytokine release syndrome), hypersensitivity
Rare	sarcoidosis
Not known	solid organ transplant rejection[f]
Endocrine disorders	
Very common	hypothyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus
Uncommon	diabetic ketoacidosis
Rare	hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome[g]
Nervous system disorders	
Very common	headache
Common	dizziness, peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis)
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis, episcleritis
Rare	Vogt-Koyanagi-Harada syndrome, serous retinal detachment

	Combination with nivolumab (with or without chemotherapy)
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia
Not known	pericardial disorders[h]
Vascular disorders	
Common	hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	cough, dyspnoea
Common	pneumonitis[a], pulmonary embolism[a], pleural effusion
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis[a], pancreatitis, stomatitis, gastritis, dry mouth
Uncommon	duodenitis
Rare	Intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders[j]
Rare	toxic epidermal necrolysis[a,d], lichen sclerosus
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e], arthralgia
Common	muscle spasms, muscular weakness, arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a]
Uncommon	tubulointerstitial nephritis, nephritis
Rare	cystitis noninfective
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema (including peripheral oedema)
Common	chest pain, pain, chills
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]
Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase

Adverse reaction frequencies presented in Table 7 may not be fully attributable to ipilimumab 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] Lichen disorders is a composite term which includes lichen keratosis and lichen planus.

Description of selected adverse reactions

Except where noted, data relating to ipilimumab monotherapy are based on patients who received either ipilimumab 3 mg/kg monotherapy (n = 131) or ipilimumab 3 mg/kg in combination with gp100 (n = 380) in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1).

Ipilimumab in combination 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 ipilimumab in combination with nivolumab than in those receiving nivolumab monotherapy. Table 8 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment. Additionally, for patients who experienced an event, Table 8 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents). The management guidelines for these adverse reactions are described in section 4.4.

Table 8: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids

	Ipilimumab in combination with nivolumab (with or without chemotherapy) %
Immune-related adverse reaction leading to permanent discontinuation	
Pneumonitis	2.1
Colitis	6
Hepatitis	5
Nephritis and renal dysfunction	1.1
Endocrinopathies	2.2
Skin	1.0
Hypersensitivity/Infusion reaction	0.3
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]	
Pneumonitis	59
Colitis	32
Hepatitis	39
Nephritis and renal dysfunction	27
Endocrinopathies	18
Skin	8
Hypersensitivity/Infusion reaction	18

[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 gastrointestinal reactions
Ipilimumab is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100.

In the ipilimumab 3 mg/kg monotherapy group, diarrhoea and colitis of any severity were reported in 27% and 8%, respectively. The frequency of severe (Grade 3 or 4) diarrhoea and severe (Grade 3 or 4) colitis was 5% each. The median time to onset of severe or fatal (Grade 3 to 5) immune-related gastrointestinal reactions was 8 weeks (range 5 to 13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution (defined as improvement to mild [Grade 1] or less or to the severity at baseline) occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks). In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration.

Immune-related colitis
In patients treated with ipilimumab in combination with nivolumab (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 ipilimumab 3 mg/kg in combination with nivolumab 1 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%).

Immune-related pneumonitis
In patients treated with ipilimumab in combination with nivolumab (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^{+}).

Immune-related hepatotoxicity
Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in < 1% of patients who received ipilimumab 3 mg/kg monotherapy.

Increases in AST and ALT of any severity were reported in 1% and 2% of patients, respectively. There were no reports of severe (Grade 3 or 4) AST or ALT elevation. Time to onset of moderate to severe or fatal (Grade 2 to 5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. With protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks. In clinical trials, liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

In patients receiving ipilimumab at a higher than recommended dose in combination with dacarbazine, immune-related hepatotoxicity occurred more frequently than in patients receiving ipilimumab 3 mg/kg monotherapy.

In patients treated with ipilimumab in combination with nivolumab (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 ipilimumab 3 mg/kg in combination with nivolumab 1 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

ipilimumab 3 mg/kg in combination with nivolumab 1 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%).

Immune-related skin adverse reactions
Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis (including SJS) has been reported in < 1% of patients who received ipilimumab in combination with gp100 (see section 5.1). Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been rarely reported with Ipilimumab in clinical studies and during post-marketing use. Incidental cases of pemphigoid have been reported during post-marketing use.

In the ipilimumab 3 mg/kg monotherapy group, rash and pruritus of any severity were each reported in 26% of patients. Ipilimumab-induced rash and pruritus were predominantly mild (Grade 1) or moderate (Grade 2) and responsive to symptomatic therapy. The median time to onset of moderate to severe or fatal (Grade 2 to 5) skin adverse reactions was 3 weeks from start of treatment (range 0.9 to 16 weeks). With protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

In patients treated with ipilimumab in combination with nivolumab (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 ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

Immune-related neurological reactions
Ipilimumab is associated with serious immune-related neurological reactions. Fatal Guillain-Barré syndrome has been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100. Myasthenia gravis-like symptoms have also been reported in < 1% of patients who received higher doses of ipilimumab in clinical trials.

Immune-related nephritis and renal dysfunction
In patients treated with ipilimumab in combination with nivolumab (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[+]).

Immune-related endocrinopathy
In the ipilimumab 3 mg/kg monotherapy group, hypopituitarism of any severity was reported in 4% of patients. Adrenal insufficiency, hyperthyroidism, and hypothyroidism of any severity were each reported in 2% of patients. The frequency of severe (Grade 3 or 4) hypopituitarism was reported in 3% of patients. Time to onset of moderate to very severe (Grade 2 to 4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with hormone replacement therapy.

In patients treated with ipilimumab in combination with nivolumab (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.

Infusion reactions
In patients treated with ipilimumab in combination with nivolumab (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 ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

Immunogenicity
Less than 2% of patients with advanced melanoma who received ipilimumab in Phase 2 and 3 clinical trials developed antibodies against ipilimumab. None had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Neutralising antibodies against ipilimumab were not detected. Overall, no apparent association was observed between antibody development and adverse reactions.

Of the patients who were treated with ipilimumab in combination with nivolumab and evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7%. Neutralising antibodies against ipilimumab ranged from 0 to 0.4%. Of the patients who were treated with ipilimumab in combination with nivolumab 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 neutralising antibodies against ipilimumab was 1.6%. Of patients evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% 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, 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, and 33.8% with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy. 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, 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks and 2.6% with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy.

When administered in combination with nivolumab, the CL of ipilimumab was unchanged in the presence of anti-ipilimumab antibodies and there was no evidence of altered toxicity profile.

Laboratory abnormalities
In patients treated with ipilimumab in combination with nivolumab (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 ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, a higher proportion of patients experienced a worsening from baseline to a Grade 3 or 4 increased ALT (15.3%).

Paediatric population

Ipilimumab as monotherapy
No new adverse drug reactions were reported in adolescents 12 years of age and older.

In study CA184070, no immune-related adverse reactions (irAR) ≥ Grade 3 were reported for the single patient 12 years of age and older who was treated with ipilimumab 3 mg/kg. Two (25.0%) of 8 patients treated with 5 mg/kg and 1 (11.1%) of 9 patients treated with 10 mg/kg reported Grade 3-4 events. None of the events were fatal. The types of irARs were consistent with the adult experience, with the most commonly reported irARs across all groups in the categories of gastrointestinal (0 [3 mg/kg], 62.5% [5 mg/kg], and 44.4% [10 mg/kg]), hepatic function (0 [3 mg/kg], 75.0% [5 mg/kg], 33.3% [10 mg/kg]), and skin (0 [3 mg/kg], 25.0% [5 mg/kg], 33.3% [10 mg/kg]) events. No new or unexpected irARs were observed in this study. No differences in the spectrum of irARs reported in adults and the paediatric population were evident.

In study CA184178, no new or unexpected irARs were observed, and the observed irARs were similar in frequency, intensity and organ site to what has been reported in adult studies. Two patients in the 10 mg/kg group experienced a Grade 1 and Grade 3 on-study endocrine irAR of hyperglycemia. No other endocrine abnormalities were reported.

A summary of adverse events in adolescents 12 years of age and older, as well as adults, is presented in Table 9.

Table 9: Summary of adverse events after up to four doses of 3, 5 and 10 mg/kg, all treated patients

	Number of patients (%)						
	Age ≥ 12 to 21 years			Age 12 to < 18 years		Adults	
	Advanced melanoma and non-melanoma solid tumours			Advanced melanoma		Advanced melanoma	
	CA184070			CA184178		CA184004/ 022 pooled	CA184004/ 007/008/022 pooled
	3 mg/kg n = 1	5 mg/kg n = 8	10 mg/kg n = 9	3 mg/kg n = 4	10 mg/kg n = 8	3 mg/kg n = 111	10 mg/kg n = 325
All deaths, n (%)	1 (100.0)	4 (50.0)	2 (22.2)	2 (50.0)	3 (37.5)	26 (23.4)	71 (21.8)
Treatment-related deaths, n (%)	0	0	0	0	0	2 (1.8)	6 (1.8)
SAEs, n (%)	1 (100.0)	7 (87.5)	4 (44.4)	1 (25.0)	6 (75.0)	50 (45.0)	168 (51.7)
SAEs, drug-related, n (%)	1 (100.0)	5 (62.5)	4 (44.4)	1 (25.0)	5 (62.5)	19 (17.1)	95 (29.2)
AEs leading to study drug discontinuation, n (%)	0	3 (37.5)	2 (22.2)	1 (25.0)	5 (62.5)	12 (10.8)	88 (27.1)
Drug-related AEs leading to study drug discontinuation, n (%)	0	3 (37.5)	2 (22.2)	1 (25.0)	5 (62.5)	9 (8.1)	61 (18.8)
irAEs, n (%)	1 (100.0)	7 (87.5)	7 (77.8)	2 (50.0)	4 (50.0)	68 (61.3)	234 (72.0)
AE, n (%)	1 (100.0)	8 (100.0)	9 (100.0)	4 (100.0)	8 (100.0)	108 (97.3)	315 (96.9)
Drug-related AEs, n (%)	1 (100.0)	7 (87.5)	9 (100.0)	2 (50.0)	7 (87.5)	88 (79.3)	274 (84.3)

MedDRA v.17.0 for CA184070, v.19.0 for CA184178, and V.12.1 for adult safety pool. NA = not assessed
For adults, deaths reported in this table are within 70 days of the last dose, regardless of relationship. Deaths for paediatric patients are those with on-study events within 30 days of the last dose, except for "all deaths," which were >30 days after the last dose. In CA184178, deaths were reported at least 90 days of the last dose.
Attribution to ipilimumab reported as possible, probable, definite, or missing for CA184178 and adult safety pool, and related or missing for CA184070.
Abbreviations: SAEs = serious adverse events; AEs = adverse events; irAEs = immune-related adverse events

Ipilimumab in combination with nivolumab
The safety of ipilimumab (1 mg/kg every 3 weeks) in combination with nivolumab (1 mg/kg or 3 mg/kg for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in 33 paediatric patients aged ≥ 1 year to < 18 years (including 20 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 ipilimumab in combination with nivolumab. No new safety signals were observed. The most common adverse reactions (reported in at least 20% of paediatric patients) for ipilimumab in combination with nivolumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for ipilimumab in combination with nivolumab were of Grades 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 74 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

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 ipilimumab in combination with nivolumab (54% and 28%, respectively). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see section 5.1). 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 ipilimumab with nivolumab (53% and 27%, respectively).

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

The maximum tolerated dose of ipilimumab has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX04.

Mechanism of action

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a key regulator of T-cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete

T-regulatory cells at the tumour site, leading to an increase in the intratumoural T-effector/ T-regulatory cell ratio which drives tumour cell death.

Pharmacodynamic effects

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase was dose-dependent. In MDX010-20 (see section 5.1), ipilimumab at 3 mg/kg with or without gp100 increased ALC throughout the induction dosing period, but no meaningful change in ALC was observed in the control group of patients who received an investigational gp100 peptide vaccine alone. In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA-DR+ CD4+ and CD8+ T cells was observed after treatment with ipilimumab, consistent with its mechanism of action. A mean increase in the percent of central memory (CCR7+ CD45RA-) CD4+ and CD8+ T cells and a smaller, but significant, mean increase in the percent of effector memory (CCR7- CD45RA-) CD8+ T cells also was observed after treatment with ipilimumab.

Clinical efficacy and safety

Ipilimumab in combination with nivolumab
For additional information on clinical efficacy and safety associated with the dosing recommendations of nivolumab when administered as monotherapy following combination therapy with ipilimumab, please refer to the nivolumab SmPC.

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 advanced melanoma and RCC.

Clinical trials with ipilimumab monotherapy

Melanoma

Overall survival (OS) advantage of ipilimumab at the recommended dose of 3 mg/kg in patients with previously-treated advanced (unresectable or metastatic) melanoma was demonstrated in a Phase 3 study (MDX010-20). Patients with ocular melanoma, primary CNS melanoma, active brain metastases, human immunodeficiency virus (HIV), hepatitis B, and hepatitis C were not included in the MDX010-20 clinical trial. Clinical trials excluded patients with ECOG performance status > 1 and mucosal melanoma. Patients without liver metastasis who had a baseline AST > 2.5 x ULN, patients with liver metastasis who had a baseline AST > 5 x ULN, and patients with a baseline total bilirubin ≥ 3 x ULN were also excluded.

For patients with a history of autoimmune disease, see also section 4.4.

MDX010-20
A Phase 3, double-blind study enrolled patients with advanced (unresectable or metastatic) melanoma who had previously been treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomised in a 3:1:1 ratio to receive ipilimumab 3 mg/kg + an investigational gp100 peptide vaccine (gp100), ipilimumab 3 mg/kg monotherapy, or gp100 alone. All patients were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. Patients were enrolled regardless of their baseline BRAF mutation status. Patients received ipilimumab every 3 weeks for 4 doses as tolerated (induction therapy). Patients with apparent tumour burden increase before completion of the induction period were continued on induction therapy as tolerated if they had adequate performance status. Assessment of tumour response to ipilimumab was conducted at approximately Week 12, after completion of induction therapy.

Additional treatment with ipilimumab (re-treatment) was offered to those who developed PD after initial clinical response (PR or CR) or after SD (per the modified WHO criteria) > 3 months from the first tumour assessment. The primary endpoint was OS in the ipilimumab+ gp100 group *vs.* the gp100 group. Key secondary endpoints were OS in the ipilimumab+ gp100 group *vs.* the ipilimumab monotherapy group and in the ipilimumab monotherapy group *vs.* the gp100 group.

A total of 676 patients were randomised: 137 to the ipilimumab monotherapy group, 403 to the ipilimumab + gp100 group, and 136 to the gp100 alone group. The majority had received all 4 doses during induction. Thirty-two patients received re-treatment: 8 in the ipilimumab monotherapy group, 23 in the ipilimumab + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across groups. The median age was 57 years. The majority (71-73%) of patients had M1c stage disease and 37-40% of patients had an elevated lactate dehydrogenase (LDH) at baseline. A total of 77 patients had a history of previously treated brain metastases.

The ipilimumab-containing regimens demonstrated a statistically significant advantage over the gp100 control group in OS. The hazard ratio (HR) for comparison of OS between ipilimumab monotherapy and gp100 was 0.66 (95% CI: 0.51, 0.87; p = 0.0026).

By subgroup analysis, the observed OS benefit was consistent within most of the subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline LDH, age, sex, and the type and number of prior therapy). However, for women above 50 years of age, the data supporting an OS benefit of ipilimumab treatment were limited. As the subgroups analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data.

Median and estimated rates of OS at 1 year and 2 years are presented in Table 10.

Table 10: Overall survival in MDX010-20

	Ipilimumab 3 mg/kg n = 137	gp100[a] n = 136
Median Months (95% CI)	10 months (8.0, 13.8)	6 months (5.5, 8.7)
OS at 1 year % (95% CI)	46% (37.0, 54.1)	25% (18.1, 32.9)
OS at 2 years % (95% CI)	24% (16.0, 31.5)	14% (8.0, 20.0)

[a] gp100 peptide vaccine is an experimental control.

In the ipilimumab 3 mg/kg monotherapy group, median OS was 22 months and 8 months for patients with SD and those with PD, respectively. At the time of this analysis, medians were not reached for patients with CR or PR.

For patients who required re-treatment, the BORR was 38% (3/8 patients) in the ipilimumab monotherapy group, and 0% in the gp100 group. The disease control rate (DCR) (defined as CR+PR+SD) was 75% (6/8 patients) and 0%, respectively. Because of the limited number of patients in these analyses, no definitive conclusion regarding the efficacy of ipilimumab re-treatment can be drawn.

The development or maintenance of clinical activity following ipilimumab treatment was similar with or without the use of systemic corticosteroids.

CA184-169

A Phase 3, double-blind study enrolled patients with previously treated or untreated unresectable Stage III or Stage IV melanoma. A total of 727 patients were randomised, 362 to receive ipilimumab 3 mg/kg and 365 to receive ipilimumab 10 mg/kg every 3 weeks for 4 doses. In the ipilimumab 10 mg/kg group, the median OS (95% CI) was 16 months (11.63, 17.84) and in the ipilimumab 3 mg/kg group the median OS (95% CI) was 12 months (9.86, 13.27). Overall survival compared between Ipilimumab 10 mg/kg and 3 mg/kg groups showed HR = 0.84 (95% CI: 0.70, 0.99;

P-value = 0.04). No statistically significant difference in progression free survival (PFS) was observed between the 10 mg/kg and the 3 mg/kg groups. (HR 0.89 with a 95% CI of 0.76, 1.04 and log-rank test P-value = 0.1548). BORR was similar in the 10 mg/kg and 3 mg/kg groups. BORR in the 10 mg/kg group was 15.3% (95% CI: 11.8, 19.5) and in the 3 mg/kg group was 12.2% (95% CI: 9.0, 16.0). Ipilimumab 10 mg/kg was associated with higher rates of adverse events compared with the 3 mg/kg dose. The frequencies of serious adverse reactions in the 10 mg/kg and 3 mg/kg groups were 37% and 18%, with the 3 most common serious adverse reactions being diarrhoea (10.7% vs 5.5%), colitis (8.0% vs 3.0%), and hypophysitis (4.4% vs 1.9%). Adverse events leading to discontinuation in the 10 mg/kg and 3 mg/kg groups occurred in 31% and 19% of patients, with AEs leading to death in 4 and 2 patients, respectively.

At the recommended dose of 3 mg/kg median OS was similar in the subgroup of females ≥ 50 years of age compared to the overall population (11.40 vs 11.53 months). Median OS in the subgroup with brain metastases at baseline was 5.67 months at the recommended dose of 3 mg/kg.

Other studies with ipilimumab monotherapy

Melanoma

CA184332 and CA184338
OS of ipilimumab 3 mg/kg monotherapy in chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials (N = 78; randomised) and in treatment-naive patients in two retrospective observational studies (N = 273 and N = 157) were generally consistent. In the two observational studies, 12.1% and 33.1% of the patients had brain metastases at the time of advanced melanoma diagnosis. Median OS and estimated 1-year, 2-year, 3-year and 4-year survival rates are presented in Table 11. The estimated 1-year, 2-year and 3-year survival rates for chemotherapy-naive patients (N = 78) pooled across Phase 2 and 3 clinical trials were 54.1% (95% CI: 42.5 - 65.6), 31.6% (95% CI: 20.7 - 42.9) and 23.7% (95% CI: 14.3 - 34.4) respectively.

Table 11: Overall survival in observational studies

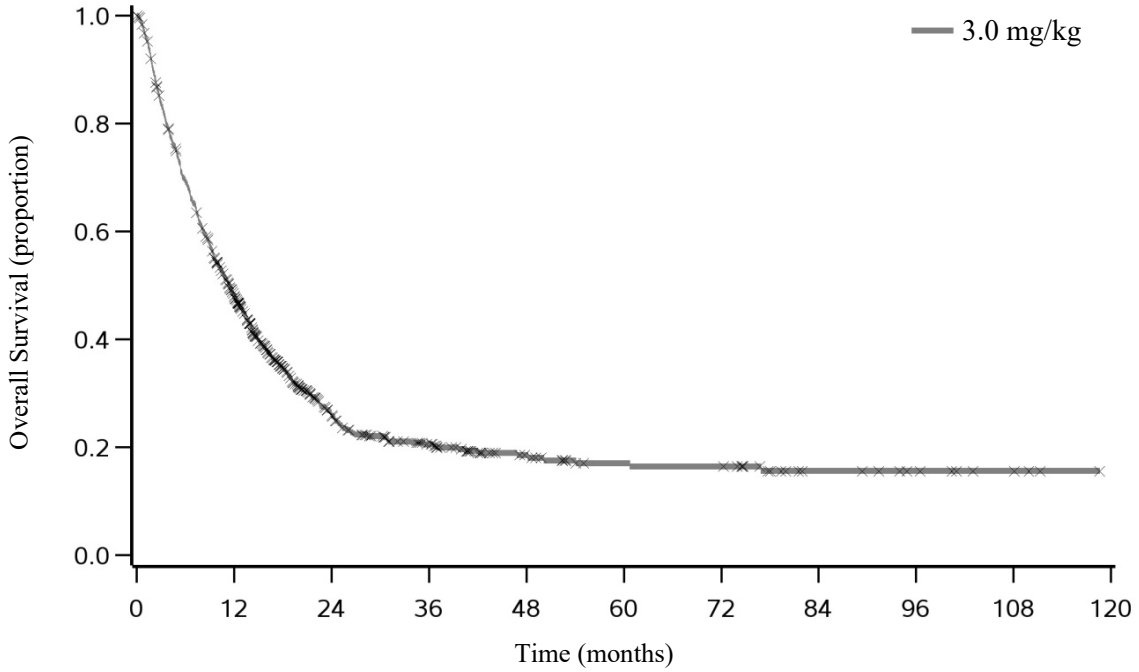
	CA184338 n = 273	CA184332 n = 157
Median OS (95% CI)	14 months (12.8-18.7)	10 months (7.0-12.8)
OS at 1 year % (95% CI)	59% (52.5-64.3)	44% (35.5, 51.4)
OS at 2 years % (95% CI)	39% (33.1-44.8)	26% (18.9-33.3)
OS at 3 years % (95% CI)	31% (25.5-36.7)	22% (15.5-29.2)
OS at 4 years % (95% CI)	26% (20.4-31.3)	22% (15.5-29.2)

Patients with brain metastases in study CA184332 had a median OS of 7 months (95% CI: 5.06 - 12.81) and patients without brain metastases had a median OS of 14.1 months (95% CI: 9.96-Not estimated).

Patients with brain metastases in study CA184338 had a median OS of 6.3 months (95% CI: 3.2 - 12.0) and patients without brain metastases had a median OS of 17.7 months (95% CI: 13.6 - 12.1).

Long term survival benefit of treatment with ipilimumab (at 3 mg/kg) is demonstrated through a pooled analysis of OS data from clinical trials in patients with previously treated and treatment naive advanced melanoma (N = 965). The Kaplan-Meier OS curve revealed a plateau beginning around year 3 (OS rate = 21% [95% CI: 17-24]) that extended up to 10 years in some patients (see Figure 1).

Figure 1: Overall survival with ipilimumab 3 mg/kg in pooled analysis



No. at Risk											
3.0 mg/kg	965	429	127	73	41	29	28	12	8	4	0

Clinical trials with ipilimumab in combination with nivolumab

Melanoma

Randomised phase 3 study of ipilimumab in combination with nivolumab or nivolumab as monotherapy vs. ipilimumab as monotherapy (CA209067)

The safety and efficacy of ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg 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.

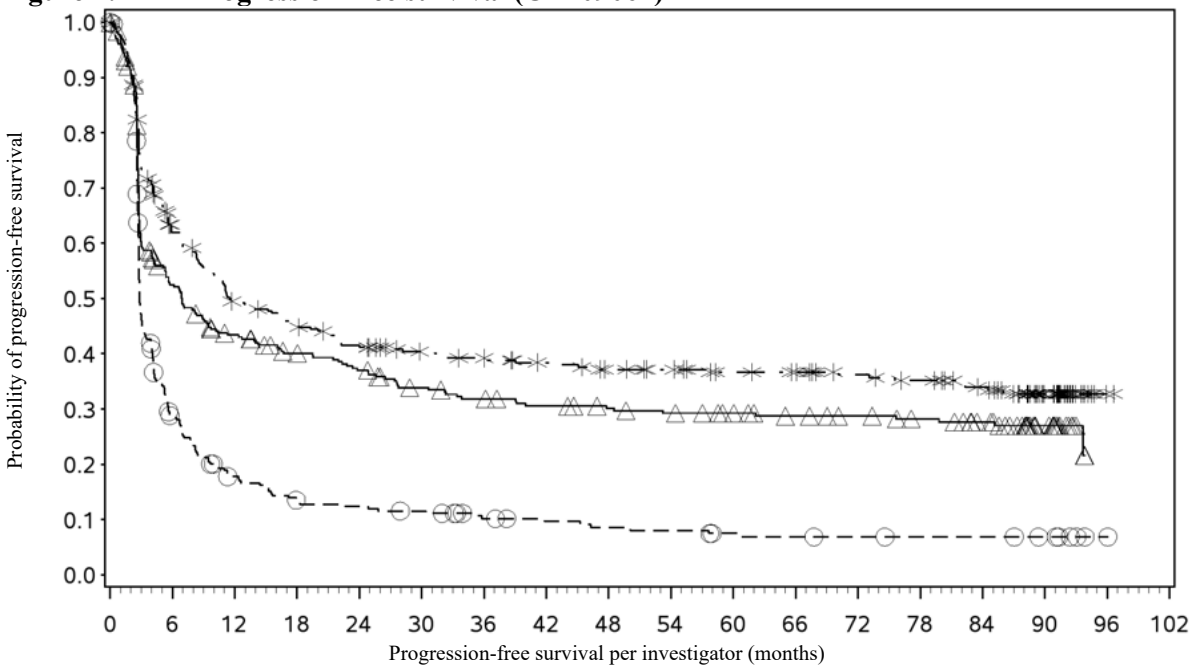
A total of 945 patients were randomised to receive ipilimumab in combination with nivolumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously 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 ipilimumab in combination with nivolumab 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)

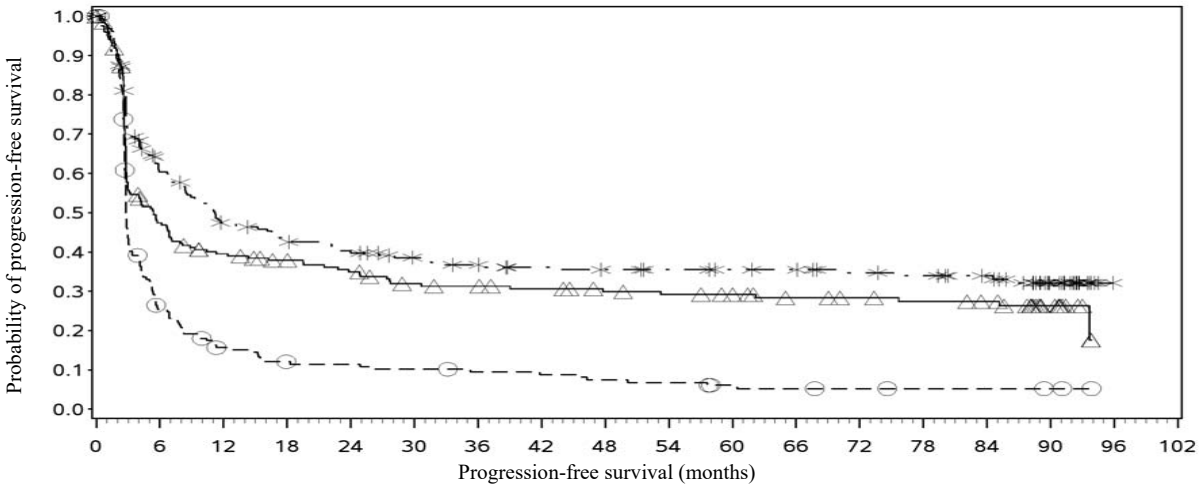
—△—— Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)

- - -○- - - 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%



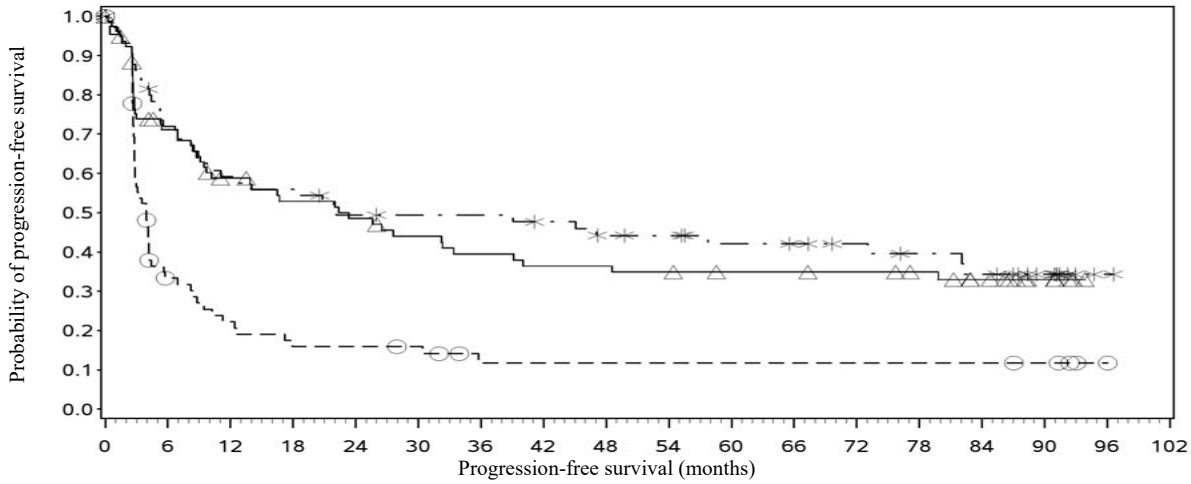
Number of subjects at risk

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

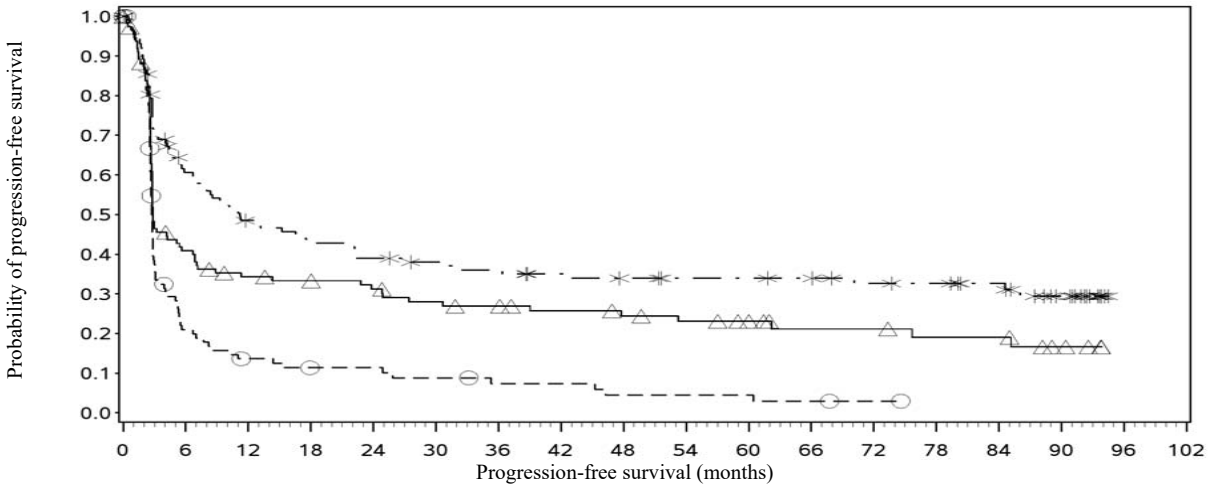
Nivolumab + ipilimumab																	
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1	-
Nivolumab																	
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0	-
Ipilimumab																	
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1	-

- - -✳- - - 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%



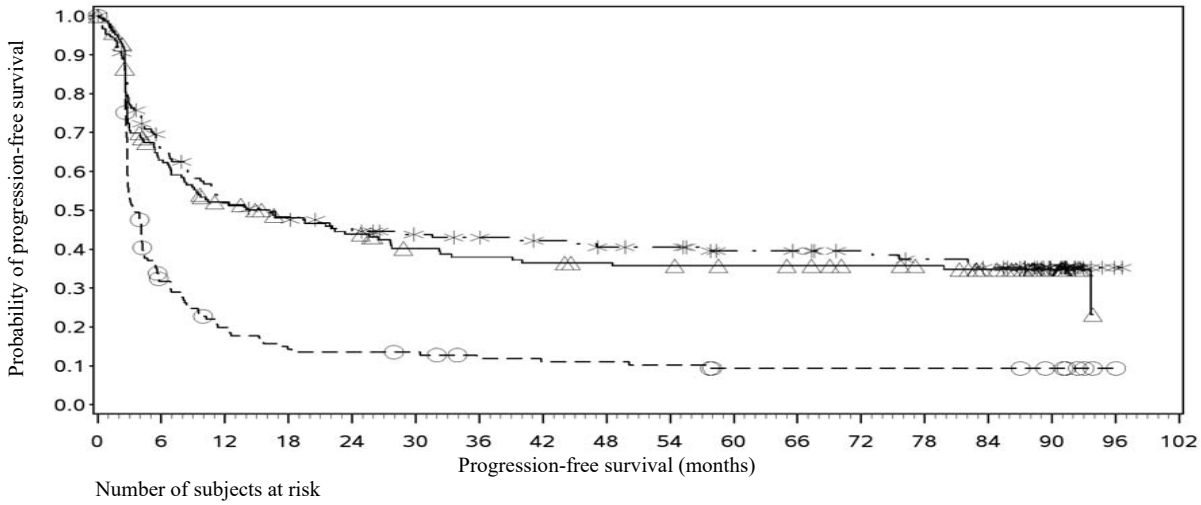
Number of subjects at risk

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)

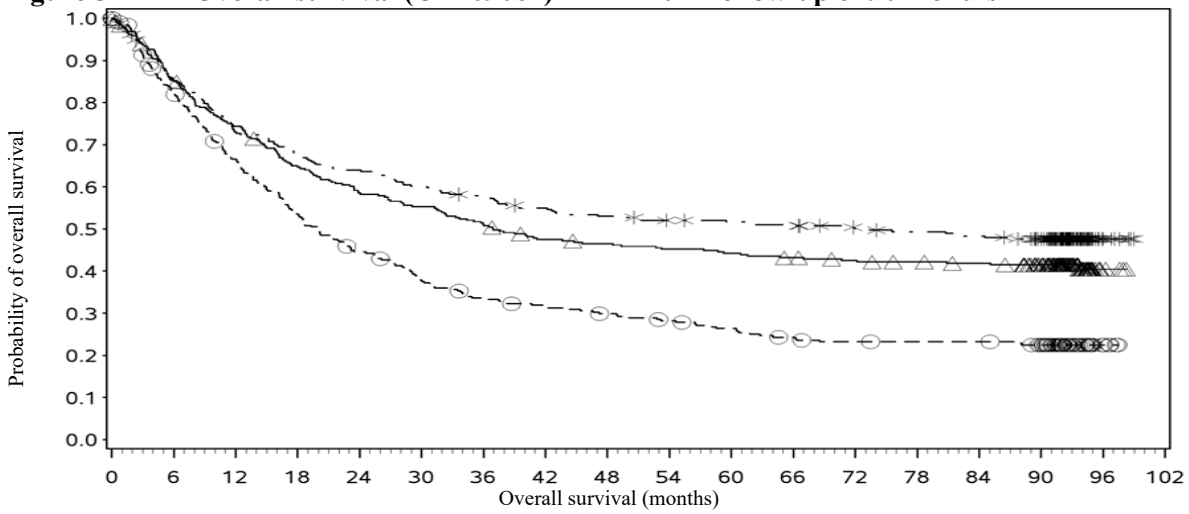
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

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 ipilimumab in combination with nivolumab 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)

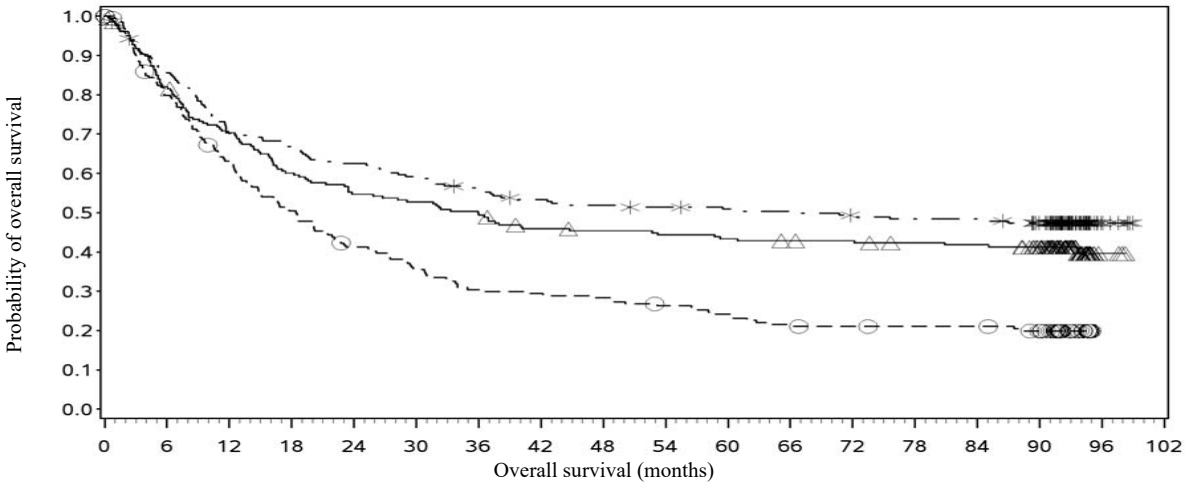
—△—— Nivolumab (events: 182/316), median and 95% CI: 36.93 months (28.25, 58.71)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57), 60 months: 44% (39, 50), and 90 months: 42% (36, 47)

- - -○- - - 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%



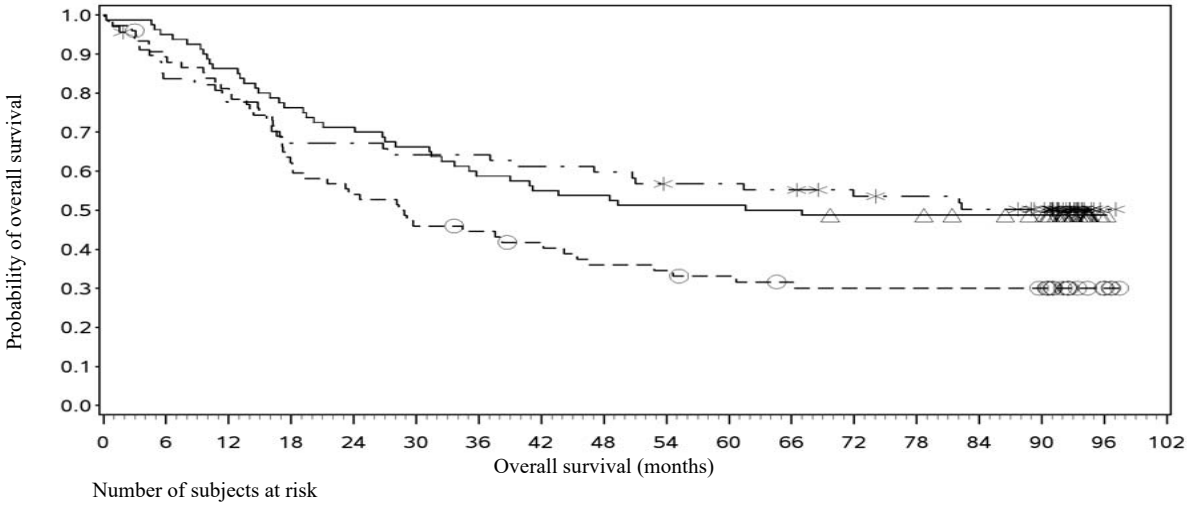
Number of subjects at risk

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

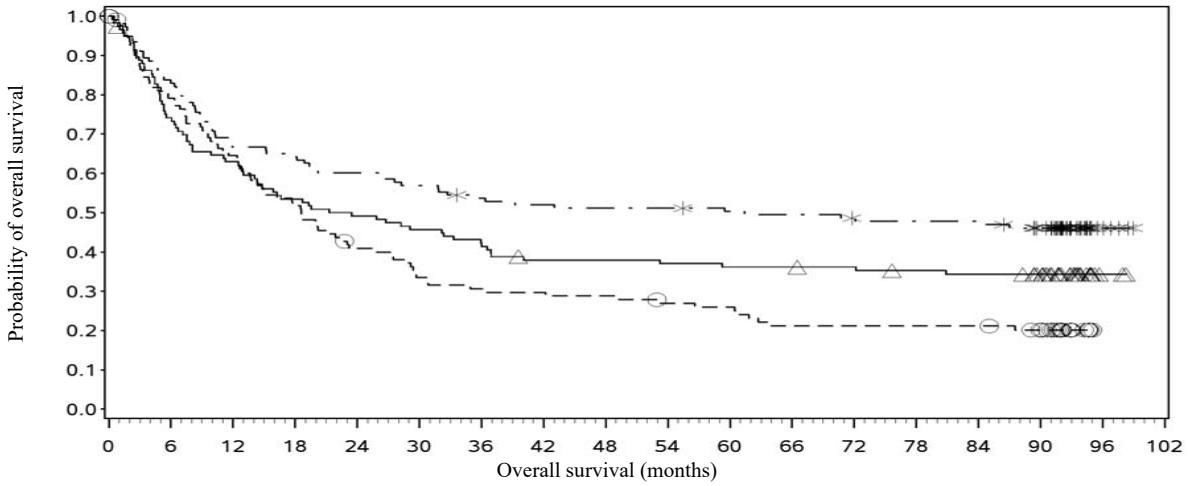
Nivolumab+ipilimumab																	
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1	-
Nivolumab																	
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1	-
Ipilimumab																	
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4	-

- - -✳- - - 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%



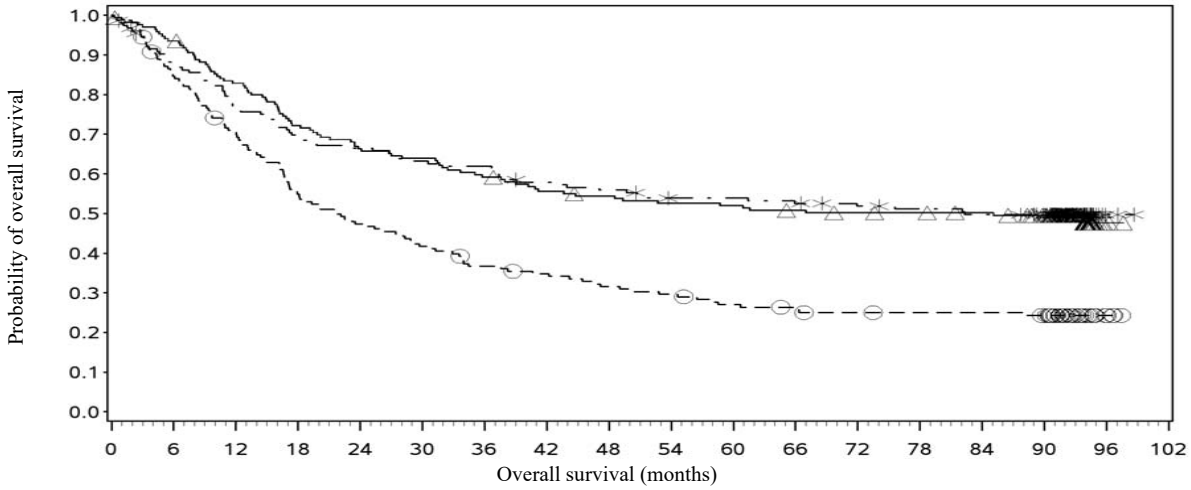
Number of subjects at risk

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.)
- - -O- - - 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 12.

Table 12: 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 12) 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 ipilimumab in combination with nivolumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.17 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 ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab 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).

Renal cell carcinoma

Randomised phase 3 study of ipilimumab in combination with nivolumab vs. sunitinib (CA209214)
The safety and efficacy of ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab 1 mg/kg (n = 425) administered intravenously over 30 minutes in combination with nivolumab administered intravenously over 60 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 Blinded Independent Central Review (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 ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day-21.4^{+} months) in ipilimumab with nivolumab- treated patients and was 7.8 months (range: 1 days-20.2^{+} months) in sunitinib-treated patients. Ipilimumab with nivolumab was continued beyond progression in 29% of patients.

Efficacy results for the intermediate/poor risk patients are shown in Table 13 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 8 (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 13: Efficacy results in intermediate/poor risk patients (CA209214)

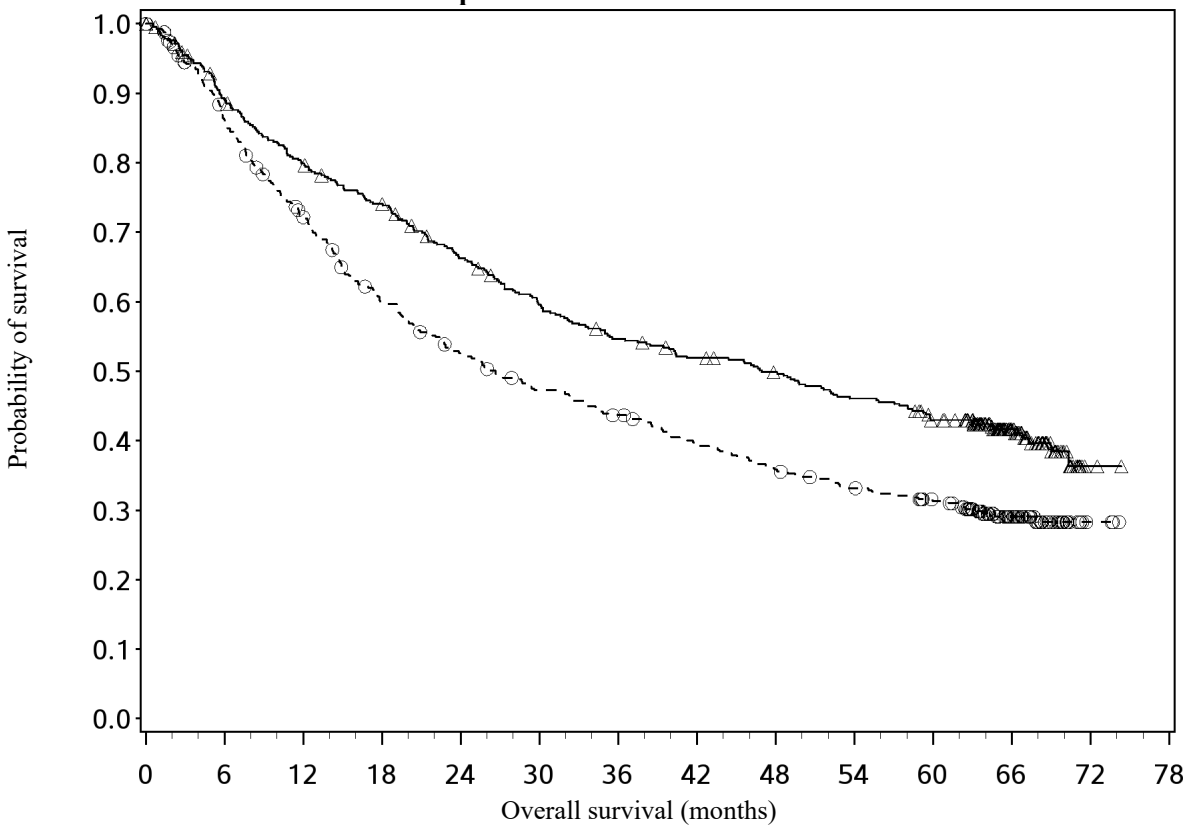
	nivolumab + ipilimumab (n = 425)		**sunitinib (n = 422)**
	Primary analysis minimum follow-up: 17.5 months		
Overall survival			
Events	140 (33%)		188 (45%)
Hazard ratio[a]		0.63	
99.8% CI		(0.44, 0.89)	
p-value[b, c]		< 0.0001	
Median (95% CI)	NE (28.2, NE)		25.9 (22.1, NE)
Rate (95% CI)			
At 6 months	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)

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)
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)
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%)

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
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 8: 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 ipilimumab in combination with nivolumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression ≥ 1% was

not reached for ipilimumab in combination with nivolumab, 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 ipilimumab in combination with nivolumab 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 ipilimumab plus nivolumab (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 ipilimumab plus nivolumab 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 ipilimumab in combination with nivolumab 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 ipilimumab and nivolumab 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.

First-line treatment of non-small cell lung cancer

Randomised phase 3 study of ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)

The safety and efficacy of ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 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 ipilimumab in combination with nivolumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the ipilimumab in combination with nivolumab and platinum-based chemotherapy arm received ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 360 mg administered intravenously over 30 minutes every 3 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.

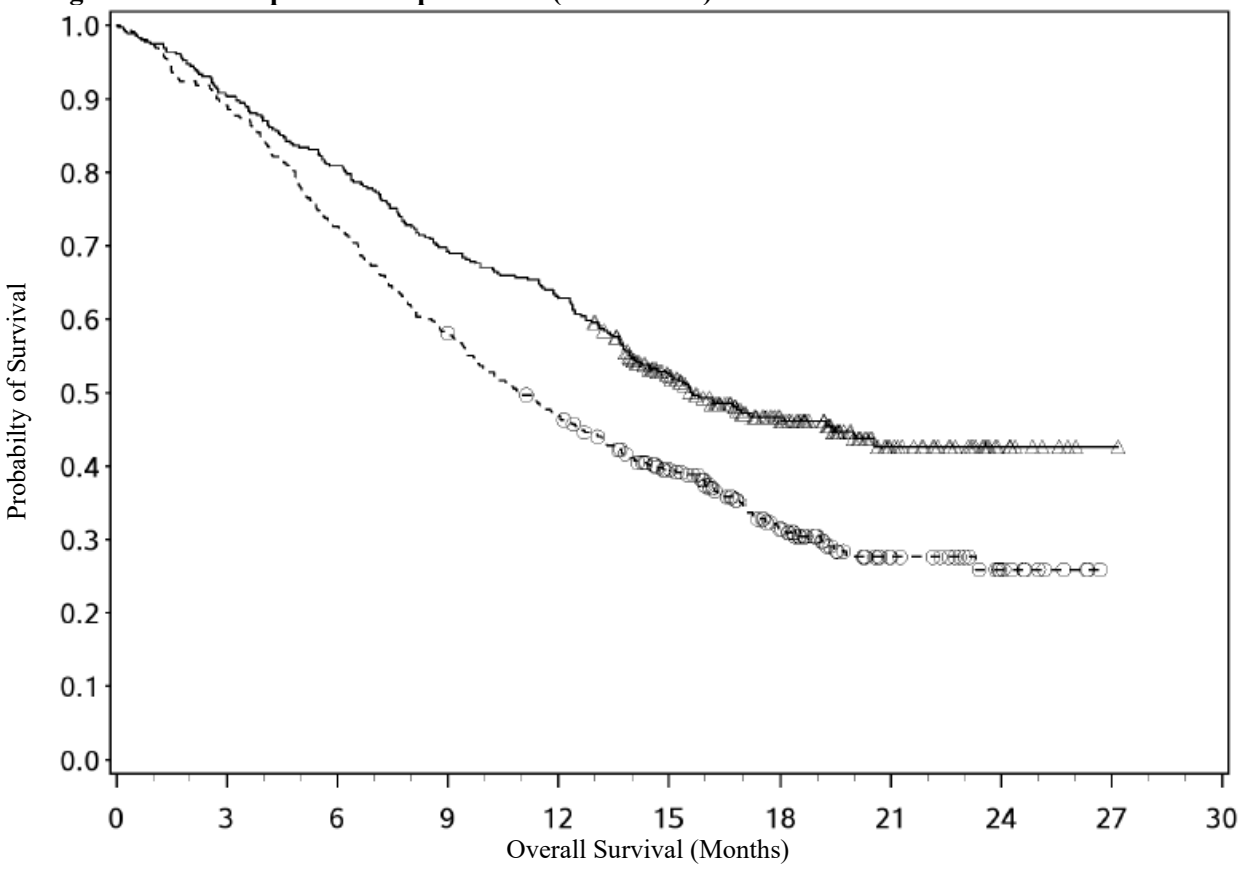
CA2099LA baseline characteristics were generally balanced across all treatment groups. The median age was 65 years (range: 26-86) with 51% ≥ 65 years of age and 10% ≥ 75 years of age. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% 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 ipilimumab in combination with nivolumab 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 9 (updated OS analysis with a minimum follow-up of 12.7 months) and Table 14 (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 9). 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 9: 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)
- - -O- - - Chemotherapy (events: 242/358), median and 95% CI: 10.91 (9.46, 12.55)

Table 14: Efficacy results (CA2099LA)

	ipilimumab + nivolumab + 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)
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)

	ipilimumab + nivolumab + chemotherapy (n = 361)		chemotherapy (n = 358)
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)	10.02		5.09
(95% CI)[d]	(8.21, 13.01)		(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 ipilimumab in combination with nivolumab 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 15 summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 15: Efficacy results by tumour PD-L1 expression (CA2099LA)

	ipilimumab + nivolumab + chemo-therapy	chemo-therapy	ipilimumab + nivolumab + chemo-therapy	chemo-therapy	ipilimumab + nivolumab + chemo-therapy	chemo-therapy	ipilimumab + nivolumab + 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 ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab and chemotherapy vs. chemotherapy within this study subgroup. ORR was 27.0% in the ipilimumab in combination with nivolumab and chemotherapy arm and 15.2% in the chemotherapy arm. Forty-three percent of patients aged ≥ 75 years discontinued treatment with ipilimumab in combination with nivolumab and

chemotherapy. Efficacy and safety data of ipilimumab in combination with nivolumab and chemotherapy are limited in this patient population.

In a subgroup analysis, a reduced survival benefit for ipilimumab in combination with nivolumab 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.

Malignant pleural mesothelioma

Randomised phase 3 study of ipilimumab in combination with nivolumab vs. chemotherapy (CA209743)
The safety and efficacy of ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 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 ipilimumab in combination with nivolumab (n = 303) or chemotherapy (n = 302). Patients in the ipilimumab in combination with nivolumab arm received ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks in combination with nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 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.

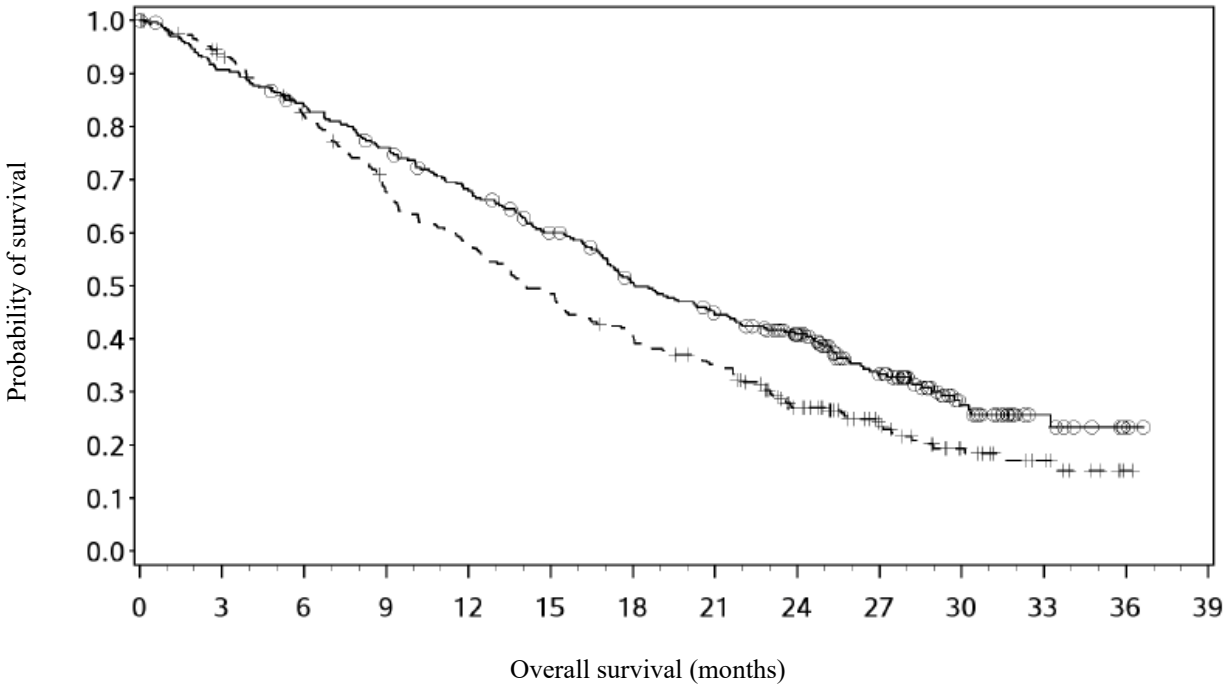
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of age. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 80% 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 BICR utilising modified RECIST criteria for pleural mesothelioma. Descriptive analyses for these secondary endpoints are presented in Table 16.

The study demonstrated a statistically significant improvement in OS for patients randomised to ipilimumab in combination with nivolumab 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 10 and Table 16.

Figure 10: 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

—O—— 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 16: Efficacy results (CA209743)

	ipilimumab + nivolumab (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)
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%

	ipilimumab + nivolumab (n = 303)	chemotherapy (n = 302)
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 17 summarises efficacy results of OS, PFS, and ORR by histology in prespecified subgroup analyses.

Table 17: Efficacy results by histology (CA209743)

	Epithelioid (n = 471)		Non-epithelioid (n = 134)	
	ipilimumab + nivolumab (n = 236)	chemotherapy (n = 235)	ipilimumab + nivolumab (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	38.6%	47.2%	43.3%	26.9%
(95% CI)[b]	(32.3, 45.1)	(40.7, 53.8)	(31.2, 56.0)	(16.8, 39.1)
Duration of response	8.44	6.83	24.02	4.21
Median (months) (95% CI)[c]	(7.16, 14.59)	(5.59, 7.13)	(8.31, N.A.)	(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 18 summarises efficacy results of OS, PFS, and ORR by baseline tumour PD-L1 expression in prespecified subgroup analyses.

Table 18: Efficacy results by tumour PD-L1 expression (CA209743)

	PD-L1 < 1% (n = 135)		PD-L1 ≥ 1% (n = 451)	
	ipilimumab + nivolumab (n = 57)	chemotherapy (n = 78)	ipilimumab + nivolumab (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 ipilimumab in combination with nivolumab arm and 79 in the chemotherapy arm). A HR of 1.02 (95% CI: 0.70, 1.48) in OS was observed for ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab was shown (see section 4.8). However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

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 ipilimumab 1 mg/kg in combination with nivolumab 240 mg 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 was 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. Randomization was stratified by tumour location (right vs left). Patients randomized to the chemotherapy arm could receive ipilimumab plus nivolumab 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 ipilimumab in combination with nivolumab arm and 84 in the chemotherapy arm. Patients in the ipilimumab plus nivolumab arm received ipilimumab 1 mg/kg every 3 weeks in combination with nivolumab 240 mg 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 ipilimumab in combination with nivolumab 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 the 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.

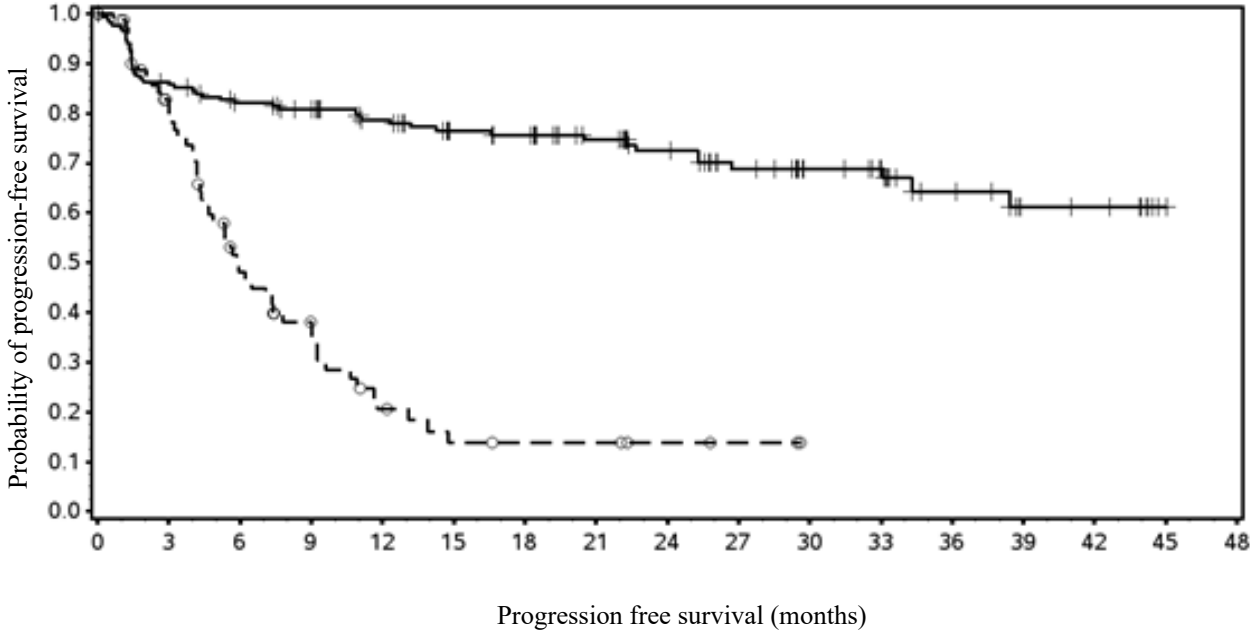
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR randomized to the ipilimumab and nivolumab arm compared with chemotherapy. The BICR-assessed PFS results are presented in Table 19 and Figure 11. 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 19: Efficacy results first-line MSI-H/dMMR centrally confirmed CRC (CA2098HW)[a]

	ipilimumab + nivolumab (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 11: 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.)
- - -O- - - 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab 1 mg/kg administered intravenously over 90 minutes in combination with nivolumab 3 mg/kg administered intravenously over 60 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 20.

Table 20: Efficacy results (CA209142) in dMMR or MSI-H CRC patients*

	ipilimumab + nivolumab (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 ipilimumab in combination with nivolumab vs. chemotherapy as first-line treatment (CA209648)

The safety and efficacy of ipilimumab in combination with nivolumab were evaluated in a randomised, active-controlled, open-label phase 3 study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (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 enrolment. 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 649 patients were randomised to receive either ipilimumab in combination with nivolumab (n = 325), or chemotherapy (n = 324), respectively. Of these, 315 patients had tumour cell PD-L1

expression ≥ 1%,158 in the ipilimumab plus nivolumab arm and 157 in the chemotherapy arm. Patients in the ipilimumab plus nivolumab arm received ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks. 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 who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent.

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%).

The primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with tumour cell PD-L1expression ≥ 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 21.

Table 21: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

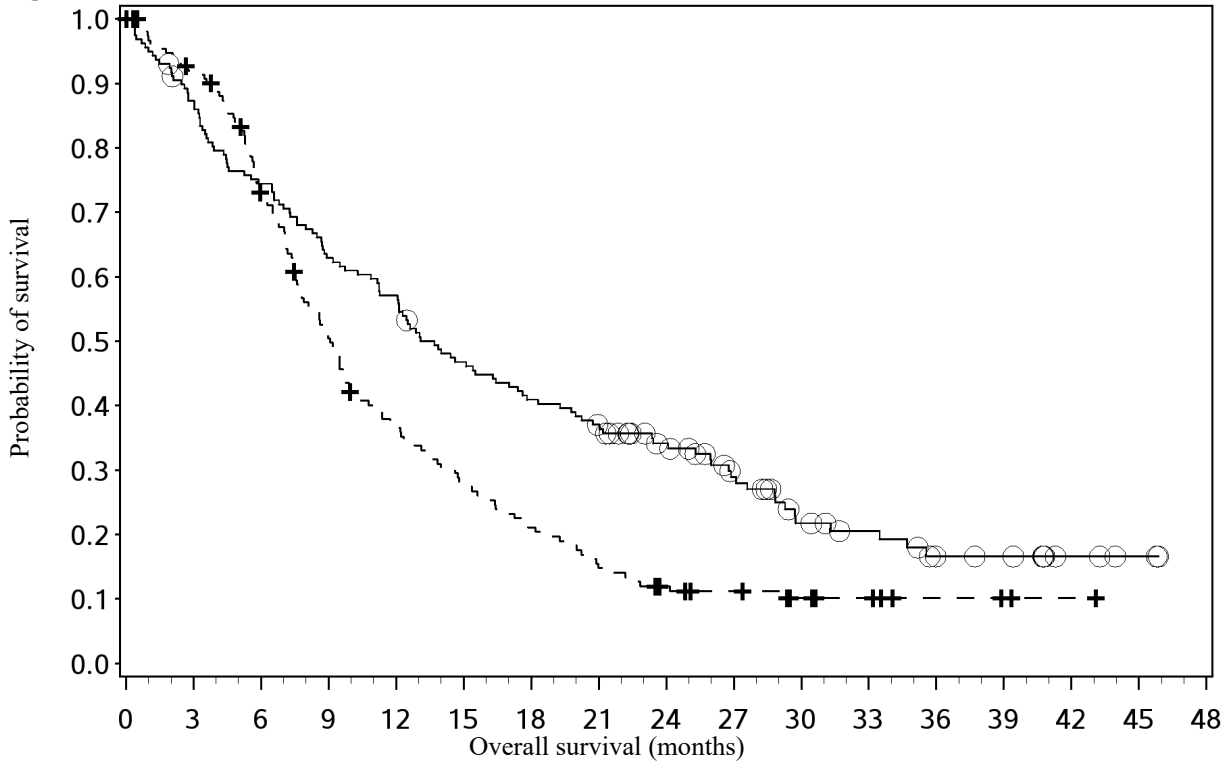
	ipilimumab + nivolumab (n = 158)	**chemotherapy[a] (n = 157)**
Overall survival		
Events	106 (67.1%)	121 (77.1%)
Hazard ratio (98.6% CI)[b]	0.64 (0.46, 0.90)	
p-value[c]	0.0010	
Median (95% CI) (months)[d]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	57.1 (49.0, 64.4)	37.1 (29.2, 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)
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 ipilimumab plus nivolumab 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 ipilimumab plus nivolumab 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 ipilimumab plus nivolumab 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 12.

Figure 12: 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

—O— 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

Hepatocellular carcinoma

The safety and efficacy of ipilimumab 3 mg/kg in combination with nivolumab 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 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 ipilimumab in combination with nivolumab (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. Patients in the ipilimumab plus nivolumab arm received ipilimumab 3 mg/kg every 3 weeks in combination with nivolumab 1 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.

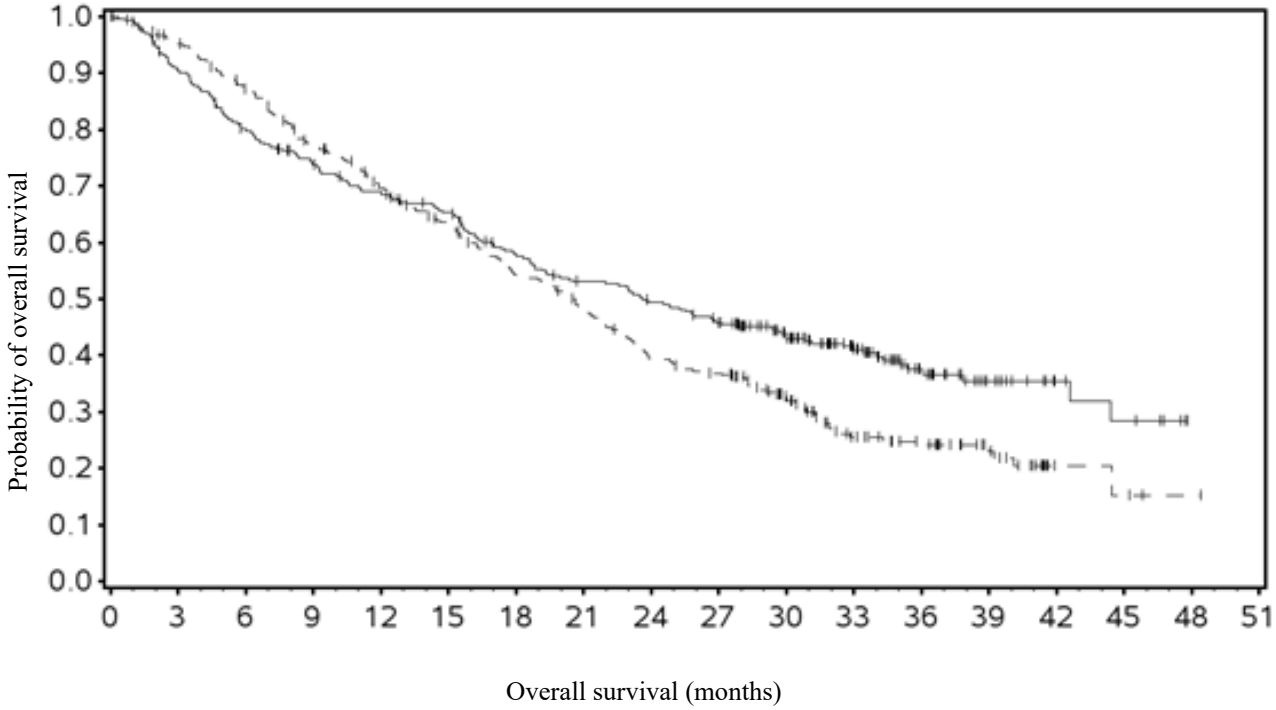
The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to ipilimumab in combination with nivolumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 22 and Figure 13.

Table 22: Efficacy results in first-line HCC (CA2099DW)[a]

	ipilimumab + nivolumab (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 13: 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

Ipilimumab as monotherapy
Study CA184070 was a multi-centre, Phase 1, open-label, dose-escalation study of ipilimumab in paediatric patients ≥ 1 year to ≤ 21 years of age with measurable/evaluable, untreatable, relapsed or refractory solid malignant tumours without a curative option with standard therapy. The study enrolled 13 patients < 12 of age and 20 patients ≥ 12 years of age. Ipilimumab was administered every 3 weeks for 4 doses and then every 12 weeks thereafter in the absence of dose limiting toxicity (DLT) and disease progression. The primary endpoints were safety and pharmacokinetics (PK). Of patients 12 years of age and older with advanced melanoma, ipilimumab 5 mg/kg was administered to three patients and ipilimumab 10 mg/kg was administered to two patients. Stable disease was achieved in two patients at the ipilimumab 5 mg/kg dose, one with a duration of > 22 months.

Study CA184178 was a non-randomised, multicenter, open-label Phase 2 study, in adolescent patients 12 to < 18 years of age with previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma. Ipilimumab was administered every 3 weeks for 4 doses. The primary efficacy endpoint was 1-year survival rate. Secondary efficacy endpoints of best overall response rate (BORR), stable disease (SD), disease control rate (DCR), and progression free survival (PFS) were based on mWHO criteria and determined by the investigator's assessment. Overall survival (OS) was also evaluated. Tumour assessment was performed at Week 12. All patients were followed for at least 1 year. Ipilimumab 3 mg/kg was administered to four patients and ipilimumab 10 mg/kg was administered to eight patients. Most patients were male (58%) and white (92%). Median age was 15 years. Stable disease was achieved for 260 days in one patient on ipilimumab 3 mg/kg and approximately 14 months in one patient on ipilimumab 10 mg/kg. Two patients treated with

ipilimumab 10 mg/kg experienced a partial response, one of which was a durable response for more than 1 year. Additional efficacy results are presented in Table 23.

Table 23: Efficacy results in CA184178

	Ipilimumab 3 mg/kg N = 4	Ipilimumab 10 mg/kg N = 8
1-year OS (%) (95% CI)	75% (12.8, 96.1)	62.5% (22.9, 86.1)
BORR (%) (95% CI)	0% (0, 60.2)	25% (3.2, 65.1)
SD (n/N)[a]	1/4	1/8
DCR (%) (95% CI)	25% (0.6, 80.6)	37.5% (8.5, 75.5)
Median PFS (months) (95% CI)	2.6 (2.3, 8.5)	2.9 (0.7,NE[a])
Median OS (months) (95% CI)	18.2 (8.9, 18.2)	Not reached (5.2, NE)

[a] NE = not estimable

Ipilimumab in combination with nivolumab

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 ipilimumab in combination with nivolumab (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 ipilimumab in combination with nivolumab 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 ipilimumab in combination with nivolumab (solid tumours other than melanoma only), no objective responses were observed. For the 33 paediatric patients treated with ipilimumab in combination with nivolumab, the median OS was 8.25 months (95% CI: 5.45, 16.95) in a descriptive analyses.

Study CA209908 was an open-label, sequential-arm, phase 1b/2 clinical study of nivolumab monotherapy and ipilimumab in combination with nivolumab 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 ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg, 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 ipilimumab in combination with nivolumab. 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 ipilimumab in combination with nivolumab. 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 improvement over what is expected in these patient populations.

5.2 Pharmacokinetic properties

The pharmacokinetics of ipilimumab was studied in 785 patients with advanced melanoma who received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. C_{max}, C_{min} and AUC of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, CL was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index 1.5 fold or less. Ipilimumab steady-state was reached by the third dose. Based on population pharmacokinetic analysis, the following mean (percent coefficient of variation) parameters of ipilimumab were obtained: terminal half-life of 15.4 days (34.4%); systemic CL of 16.8 ml/h (38.1%); and volume of distribution at steady-state of 7.47 l (10.1%). The mean (percent coefficient of variation) ipilimumab C_{min} achieved at steady-state with a 3 mg/kg induction regimen was 19.4 µg/ml (74.6%).

Ipilimumab CL increased with increasing body weight and with increasing LDH at baseline; however, no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis. CL was not affected by age (range 23-88 years), gender, concomitant use of budesonide or dacarbazine, performance status, HLA-A2*0201 status, mild hepatic impairment, renal impairment, immunogenicity, and previous anticancer therapy. The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups. No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

Based on an exposure-response analysis in 497 patients with advanced melanoma, OS was independent of prior systemic anti-cancer therapy and increased with higher ipilimumab Cminss plasma concentrations.

YERVOY in combination with nivolumab: When ipilimumab 1 mg/kg was administered in combination with nivolumab 3 mg/kg, the CL of ipilimumab was decreased by 1.5% and the CL of nivolumab was increased by 1% which were not considered clinically relevant. When ipilimumab 3 mg/kg was administered in combination with nivolumab 1 mg/kg, the CL of ipilimumab was increased by 9% and the CL of nivolumab was increased by 29%, which was not considered clinically relevant.

When administered in combination with nivolumab, the CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies and the CL of nivolumab increased by 20% in the presence of presence of anti-nivolumab antibodies. These changes were not considered clinically relevant.

YERVOY in combination with nivolumab and chemotherapy: When ipilimumab 1 mg/kg every 6 weeks was administered in combination with nivolumab 360 mg every 3 weeks and with 2 cycles of chemotherapy, the CL of ipilimumab increased approximately 22% and the CL of nivolumab decreased approximately 10%, which was not considered clinically relevant.

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild and moderate renal impairment did not influence the CL of ipilimumab.

Clinical and pharmacokinetic data with pre-existing severe renal impairment are limited; the potential need for dose adjustment cannot be determined.

Hepatic impairment

In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild hepatic impairment did not influence the CL of ipilimumab. Clinical and pharmacokinetic data with pre-existing moderate hepatic impairment are limited; the potential need for dose adjustment cannot be determined. No patients with pre-existing severe hepatic impairment were identified in clinical studies.

Paediatric population

For ipilimumab monotherapy, based on a population PK analysis using available pooled data from 565 patients from 4 phase 2 adult studies (N = 521) and 2 paediatric studies (N = 44), CL of ipilimumab increased with increasing baseline body weight. Age (2-87 years) had no clinically important effect on the CL of ipilimumab. The estimated geometric mean CL is 8.72 ml/h in adolescent patients aged ≥ 12 to < 18 years. Exposures in adolescents are comparable with those in adults receiving the same mg/kg dose. Based on the simulation in adults and paediatrics, comparable exposure is achieved in adults and paediatrics at the recommended dose of 3 mg/kg every 3 weeks.

For ipilimumab in combination with nivolumab, the exposures of ipilimumab and nivolumab in paediatric patients 12 years of age and older are expected to be comparable to that in adult patients at the recommended dose.

5.3 Preclinical safety data

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently (~3%) and included colitis (which resulted in a single fatality), dermatitis, and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate). A decrease in the weight of the thyroid and testes was seen in one study without accompanying histopathologic findings; the clinical relevance of this finding is unknown.

The effects of ipilimumab on prenatal and postnatal development were investigated in a study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through delivery, at exposure (AUC) levels either similar to or higher than those associated with the clinical dose of 3 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, both ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and infant mortality relative to control animals; these findings were dose-dependent. Additionally, developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed *in utero* to ipilimumab. One female infant had unilateral renal agenesis of the left kidney and ureter, and one male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal oedema. The relationship of these malformations to treatment is unclear.

Studies to evaluate the mutagenic and carcinogenic potential of ipilimumab have not been performed. Fertility studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride)
Sodium chloride
Mannitol (E421)
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80
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.

6.3 Shelf life

Unopened vial

3 years

After opening

From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 and 4 mg/ml) has been demonstrated for 24 hrs at 25°C and 2°C to 8°C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours in a refrigerator (2°C to 8°C) or at room temperature (20°C to 25°C).

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 first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml of concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.
40 ml of concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.

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.

Calculating the dose:

Ipilimumab monotherapy or ipilimumab in combination with nivolumab:
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of YERVOY concentrate may be needed to give the total dose for the patient.

- Each 10 ml vial of YERVOY concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab.
- The total ipilimumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of YERVOY concentrate to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Preparing the infusion:

Take care to ensure aseptic handling when you prepare the infusion.

YERVOY can be used for intravenous administration either:
- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the YERVOY concentrate, you can use either:
  - sodium chloride 9 mg/ml (0.9%) solution for injection; or
  - 50 mg/ml (5%) glucose solution for injection

STEP 1
- Allow the appropriate number of vials of YERVOY to stand at room temperature for approximately 5 minutes.
- Inspect the YERVOY concentrate for particulate matter or discoloration. YERVOY concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of YERVOY concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous bag (PVC or non-PVC).
- 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.

Administration:

The YERVOY infusion must not be administered as an intravenous push or bolus injection. Administer the YERVOY infusion intravenously over a period of 30 minutes.

The YERVOY 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).

The YERVOY infusion is compatible with:
- PVC infusion sets
- Polyethersulfone (0.2 µm to 1.2 µm) and nylon (0.2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion.

Any unused medicinal product or waste material should be discarded 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 NUMBERS

EU/1/11/698/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011
Date of latest renewal: 21 April 2016

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(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Lotte Biologics USA, LLC
6000 Thompson Road
East Syracuse, New York 13057
United States

Samsung Biologics Co. Ltd
300, Songdo Bio Way (Daero)
Yeonsu-gu, Incheon 21987
Korea

Name and address of the manufacturer(s) responsible for batch release

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
Italy

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 periodic safety update reports 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 Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe YERVOY are provided with/have access to the following to provide to their patients:

- Patient Card

Key elements for the Patient Card:

- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and need to be addressed immediately
- Request to inform the physician of all medical conditions before treatment.
- Description of the main symptoms of irARs and severe infusion reactions and the importance of notifying their treating physician immediately if symptoms occur, persist or worsen.
    - Gastrointestinal: diarrhoea, bloody stool, abdominal pain, nausea, or vomiting
    - Liver: yellowing of your skin or whites of your eyes, bleeding, dark urine
    - Skin: rash, blisters and/or peeling, mouth sores
    - Nerves: weakness, numbness or tingling in legs, arms or face
    - Hormone glands: weight change, headache, feeling tired, dizziness or fainting, changes in behavior, such as less sex drive, being irritable or forgetful, excessive hunger and/or thirst, change in amount and/or frequency of urine
    - Lungs: shortness of breath, cough, chest pain
    - Eye: blurred vision, vision changes, eye pain,
    - Severe infusion reactions: fever, chills, flushing, shortness of breath
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional first.
- Placeholder including the weblink of the Package Leaflet on the EMA website
- The importance of carrying the detachable wallet-sized Patient Card at all times to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with ipilimumab.

The Marketing Authorisation Holder shall agree the format and content of the above material with the National Competent Authority prior to launch in the Member State.

- **Obligation to conduct post-authorisation measure**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for solution for infusion
Ipilimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 5 mg ipilimumab.
Each vial contains 50 mg ipilimumab.
Each vial contains 200 mg ipilimumab.

3. LIST OF EXCIPIENTS

Excipients: Tris hydrochloride, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

50 mg/10 ml
200 mg/40 ml

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before 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

For single use only.

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/1/11/698/001
EU/1/11/698/002

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

YERVOY 5 mg/ml sterile concentrate
Ipilimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 5 mg ipilimumab.
Each vial contains 50 mg ipilimumab.
Each vial contains 200 mg ipilimumab.

3. LIST OF EXCIPIENTS

Excipients: Tris hydrochloride, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

50 mg/10 ml
200 mg/40 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV use.
Read the package leaflet before 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

For single use only.

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/1/11/698/001
EU/1/11/698/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

YERVOY 5 mg/ml concentrate for solution for infusion
ipilimumab

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.
- 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 YERVOY is and what it is used for
2. What you need to know before you use YERVOY
3. How to use YERVOY
4. Possible side effects
5. How to store YERVOY
6. Contents of the pack and other information

1. What YERVOY is and what it is used for

YERVOY contains the active substance ipilimumab, a protein which helps your immune system to attack and destroy cancer cells by your immune cells.

Ipilimumab alone is used to treat advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older.

Ipilimumab in combination with nivolumab is used to treat
- advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- malignant pleural mesothelioma (a type of cancer that affects the lining of the lung) in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- unresectable or advanced hepatocellular carcinoma (liver cancer) in adults.

Ipilimumab in combination with nivolumab and chemotherapy is used to treat advanced non-small cell lung cancer (a type of lung cancer) in adult.

As YERVOY 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 YERVOY

You should not be given YERVOY
- if you are **allergic** to ipilimumab 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 YERVOY 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.

- **Inflammation of the intestines (colitis)** which can worsen to bleedings or bowel perforation. Signs and symptoms of colitis may include diarrhoea (watery, loose or soft stools), an increased number of bowel movements than usual, blood in your stools or darker-coloured stools, pain or tenderness in your stomach area.

- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).

- **Inflammation of the liver (hepatitis)** that can lead to liver failure. Signs and symptoms of hepatitis may include eye or skin yellowing (jaundice), pain on the right side of your stomach area, tiredness.

- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis, Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)). Signs and symptoms of severe skin reaction may include such as skin rash with or without itching, peeling of the skin, dry skin, fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells) and effects on liver, kidneys or lungs. Please note that the reaction called DRESS may develop weeks or months after your last dose.

- **Inflammation of the nerves** that can lead to paralysis. Symptoms of nerve problems may include muscle weakness, numbness or tingling in your hands or feet, loss of consciousness or difficulty waking up.

- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.

- **Inflammation of hormone producing glands** (especially the pituitary, adrenal and thyroid glands) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include headaches, blurry or double vision, tiredness, decreased sexual drive, behavioural changes.

- **Type 1 Diabetes, including diabetic ketoacidosis** (acid in the blood produced from diabetes).

- **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.

- **Inflammation of the eyes.** Signs and symptoms may include redness in the eye, pain in the eye, vision problems, blurry vision or temporary loss of sight.

- **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.

- **Organ transplant rejection.**

Tell your doctor immediately if you have any of these signs or symptoms or they get worse. **Do not try to treat your symptoms with other medicines.** Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms, withhold the next dose of YERVOY, or stop your treatment with YERVOY 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 treatment.

Check with your doctor or nurse before you are given YERVOY
- if you have an **autoimmune disease** (a condition where the body attacks its own cells);
- if you have, or have ever had, **chronic viral infection of the liver**, including hepatitis B (HBV) or hepatitis C (HCV);
- if you have **human immunodeficiency virus** (HIV) infection or acquired immune deficiency syndrome (AIDS).
- if you have previously experienced a severe skin adverse reaction on a prior cancer therapy.
- if you have any history of inflammation of the lungs

Children and adolescents
YERVOY 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 YERVOY
Before you are given YERVOY, tell your doctor
- if you are taking any medicines that suppress your immune system, such as corticosteroids. These medicines may interfere with the effect of YERVOY. However, once you are treated with YERVOY, your doctor may give you corticosteroids to reduce the side-effects that you may have with YERVOY.

- if you are taking any medicines that stop your blood from clotting (anticoagulants). These medicines may increase the likelihood of bleeding in the stomach or intestine, which is a side-effect of YERVOY.

- if you have recently been prescribed Zelboraf (vemurafenib, another medicine for the treatment of skin cancer). When YERVOY is given following prior vemurafenib there may be an increased risk of skin side-effects.

Also 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. Based on early data, the combination of YERVOY (ipilimumab) and vemurafenib is not recommended due to increased toxicity to the liver.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant, if you are planning to become pregnant, or if you are breast-feeding.

You must not use YERVOY if you are pregnant unless your doctor specifically recommends it. The effects of YERVOY in pregnant women are not known, but it is possible that the active substance, ipilimumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with YERVOY if you are a woman who could become pregnant.
- If you become pregnant while using YERVOY **tell your doctor**.

It is not known whether ipilimumab gets into breast milk. However, significant exposure of ipilimumab to the infant through breast milk is not expected and no effects on the breast-fed infant are anticipated. Ask your doctor if you can breast-feed during or after treatment with YERVOY.

Driving and using machines
Do not drive, cycle or use machines after you have been given YERVOY unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of YERVOY. This can affect your ability to drive, cycle or to use machines.

YERVOY contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given YERVOY.

This medicine contains 23 mg sodium (main component of cooking/table salt) in each 10 ml vial. This is equivalent to 1.15% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 92 mg sodium (main component of cooking/table salt) in each 40 ml vial. This is equivalent to 4.60% of the recommended maximum daily dietary intake of sodium for an adult

3. How to use YERVOY

How YERVOY is given
YERVOY will be given to you in a hospital or clinic under the supervision of an experienced doctor.

When YERVOY is given alone for the treatment of skin cancer, YERVOY will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 minutes.

When YERVOY is given in combination with nivolumab for the treatment of skin cancer, you will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab 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 YERVOY is given in combination with nivolumab for the treatment of advanced kidney cancer, you will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab 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 YERVOY is given in combination with nivolumab for the treatment of advanced colon or rectal cancer in adults, you will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab will be given as an infusion over a period of 30 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of malignant pleural mesothelioma or advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes every 6 weeks.

When YERVOY is given in combination with nivolumab for the treatment of 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, nivolumab will be given as an infusion over a period of 30 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When YERVOY is given in combination with nivolumab 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 6 weeks. After completion of 2 cycles of chemotherapy, ipilimumab will be given in combination with nivolumab as an infusion over a period of 30 minutes every 6 weeks.

How much YERVOY is given
When YERVOY is given alone for the treatment of skin cancer, the recommended dose is 3 mg of ipilimumab per kilogram of your body weight.

The amount of YERVOY you will be given will be calculated based on your body weight. Depending on your dose, some or all of the content of the YERVOY vial may be diluted with sodium

chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection before use. More than one vial may be necessary to obtain the required dose.

You will be treated with YERVOY once every 3 weeks, for a total of 4 doses. You may notice the appearance of new lesions or growth of existing lesions on your skin, which can be expected when you are being treated with YERVOY. Your doctor will continue giving you YERVOY for a total of 4 doses, depending on your tolerance to the treatment.

When YERVOY is given in combination with nivolumab for the treatment of skin cancer in adults and adolescents 12 years of age and older, the recommended dose of YERVOY is 3 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter the recommended dose of nivolumab (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 YERVOY is given in combination with nivolumab for the treatment of advanced kidney cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter, the recommended dose of nivolumab is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of advanced colon or rectal cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter, the recommended dose of nivolumab is 240 mg given every 2 weeks or 480 mg every 4 weeks (single-agent phase) depending on your treatment.

When YERVOY is given in combination with nivolumab for the treatment of malignant pleural mesothelioma or advanced oesophageal cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 6 weeks.

When YERVOY is given in combination with nivolumab for the treatment of unresectable or advanced liver cancer, the recommended dose of YERVOY is 3 mg of ipilimumab per kilogram of your body weight for up to 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of nivolumab is 240 mg given every 2 weeks or 480 mg every 4 weeks (single agent phase) depending on your treatment.

When YERVOY is given in combination with nivolumab and chemotherapy for the treatment of advanced non-small cell lung cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight. You will be given an infusion over a period of 30 minutes, every 6 weeks.

If you miss a dose of YERVOY
It is very important for you to keep all your appointments to receive YERVOY. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using YERVOY
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with YERVOY unless you have discussed this with your doctor.

If you have any further questions about your treatment or the use of this medicine, ask your doctor.

When YERVOY is given in combination with nivolumab or in combination with nivolumab and chemotherapy, you will first be given nivolumab followed by YERVOY and then by chemotherapy.

Please refer to the package leaflet of the other anti-cancer medicines in order to understand the use of these other medicines. If you have questions about these medicines, 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
YERVOY 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.

The following side effects have been reported in patients receiving 3 mg/kg ipilimumab alone:

Very common (may affect more than 1 in 10 people)
- loss of appetite
- diarrhoea (watery, loose or soft stools), vomiting or feeling sick (nausea), constipation, stomach pain
- skin rash, itching
- pain in the muscles, bones, ligaments, tendons, and nerves
- feeling tired or weak, reaction at site of injection, fever, oedema (swelling), pain

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)
- serious bacterial infection of the blood (sepsis), infection of the urinary tract, infection of the respiratory tract
- tumour pain
- 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 function of the thyroid gland which can cause tiredness or weight gain, underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain
- dehydration
- confusion, depression
- excessive accumulation of fluid in the brain, damage to the nerves (causing pain, weakness and cramps), dizziness, headache,
- blurred vision, pain in the eye
- irregular or abnormal heart beat
- low blood pressure, temporary redness of the face and neck, feeling of intense heat with sweating and rapid heart beat
- shortness of breath (dyspnoea), cough, hay fever
- bleeding in the stomach or intestine, inflammation of the intestines (colitis), heartburn, mouth ulcers and cold sores (stomatitis)
- abnormal function of the liver
- inflammation of the inner surface lining of a particular organ
- inflammation and redness of the skin, skin colour change in patches (vitiligo), hives (itchy, bumpy rash), hair loss or thinning, excessive sweating at night, dry skin
- pain in muscles and joints(arthralgia), muscle spasms, inflammation of the joints (arthritis)
- kidney function failure
- shivering, lack of energy

- flu-like illness
- decrease in body weight

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)
- serious bacterial infection of the blood (septic shock), inflammation around the brain or spinal cord, inflammation of the stomach and intestines, inflammation of bowel wall (causing fever, vomiting and stomach pain), lung infection (pneumonia)
- a group of symptoms due to cancer in the body such as high blood levels of calcium and cholesterol, and low blood levels of sugar (paraneoplastic syndrome)
- increase of eosinophils (type of white blood cells)
- allergic reaction
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), overactive function of the thyroid gland, which can cause rapid heart rate, sweating and weight loss, defect of the glands producing sex hormones
- decreased function of the adrenal glands caused by an underactive hypothalamus (part of the brain)
- 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).
- changes in mental health, lowered sex drive
- severe and possibly fatal inflammation of the nerves causing pain, weakness or paralysis in the extremities (Guillain-Barré syndrome), fainting, inflammation of the nerves within the brain, difficulty in coordinating movements (ataxia), shaking, brief involuntary muscle contraction, difficulty in speaking
- inflammation of the eye (conjunctivitis), bleeding in the eye, inflammation of the coloured part of the eye, reduced vision, a foreign body sensation in the eyes, swollen runny eyes, swelling of the eye, inflammation of the eyelids
- inflammation of the blood vessels, disease of the blood vessels, restriction in the blood supply to the extremities, low blood pressure when standing up
- extreme difficulty in breathing, fluid accumulation in the lungs, inflammation of the lungs
- bowel perforation, inflammation of the small intestine, inflammation of the bowel or the pancreas (pancreatitis), peptic ulcer, inflammation of the food pipe, blockage of the intestines, inflammation of the anus and the rectal wall (marked by bloody stools and a frequent urge to defecate)
- liver failure, inflammation of the liver, enlarged liver, yellowing of the skin or eyes (jaundice)
- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)
- inflammation of the muscles causing pain or stiffness in the hip and shoulder
- inflammation of the kidney, or the central nervous system
- multi organ inflammation
- inflammation of skeletal muscles
- muscle weakness
- kidney disease
- absence of menstrual periods
- multi organ dysfunction, reaction related to infusion of the medicine
- change in hair colour
- 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

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Rare (may affect up to 1 in 1 000 people)
- inflammatory disease of blood vessels (most commonly head arteries)
- swelling of the thyroid gland (thyroiditis)
- skin disease characterised by dry red patches covered with scales (psoriasis)

- inflammation and redness of the skin (erythema multiforme)
- a type of severe skin reaction characterised by rash accompanied by one or more of the following features: fever, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidneys or lungs (a reaction called DRESS).
- 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), loosening of membrane at the back of the eye (serous retinal detachment)
- symptoms of type 1 diabetes or diabetic ketoacidosis include feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, feeling tired, feeling sick, stomach pain, fast and deep breathing, confusion, unusual sleepiness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat
- muscle weakness and tiredness without atrophy (myasthenia gravis)
- Lack or reduction of digestive enzymes made by pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Very rare (may affect up to 1 in 10 000 people)
- serious, potential life-threatening allergic reaction

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

In addition, the following uncommon (may affect up to 1 in 100 people) side effects have been reported in patients who received doses other than 3 mg/kg of YERVOY in clinical trials:

- triad of symptoms (meningism): neck stiffness, intolerance of bright light and headache, flu-like discomfort
- inflammation of the heart muscle, weakness of the heart muscle, fluid around the heart
- inflammation of the liver or the pancreas, nodules of inflammatory cells in various organs of your body
- infection within the abdomen
- painful skin lesions of the arms and legs and face (erythema nodosum)
- overactive pituitary gland
- decreased function of the parathyroid gland
- inflammation of the eye, eye muscle inflammation
- decreased hearing
- poor blood circulation which makes toes and fingers numb or pale
- damage to the tissues of the hands and feet resulting in redness, swelling and blisters

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- organ transplant rejection
- a type of skin blistering disease (called pemphigoid)

- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis). Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.
- 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)

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Changes in test results
YERVOY may cause changes in the results of tests carried out by your doctor. These include:
- a variation in the 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)
- an abnormal variation of hormones and liver enzyme levels in the blood
- abnormal liver function test
- abnormal levels of calcium, sodium, phosphate or potassium in the blood
- presence of blood or proteins in the urine
- an abnormally high alkalinity of the blood and other body tissues
- kidneys unable to remove acids from blood normally
- presence of antibodies in the blood against some of your own cells

The following side effects have been reported **with ipilimumab 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
- underactive thyroid gland (which can cause tiredness or weight gain)
- 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)
- loss of appetite, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- headache
- shortness of breath (dyspnoea), cough
- diarrhoea (watery, loose or soft stools), vomiting or feeling sick (nausea), stomach pain, constipation
- skin rash sometimes with blisters, itching
- pain in the muscles and bones (musculoskeletal pain), painful joints (arthralgia)
- feeling tired or weak, fever, oedema (swelling)

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)
- lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- increase of eosinophils (type of white blood cells)
- allergic reaction, reactions related to the infusion of the medicine
- overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), 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 albumin and phosphate in the blood, decrease in body weight
- inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- blurred vision, dry eye
- rapid heart beat, changes in the rhythm or rate of the heartbeat, irregular or abnormal heart beat

- 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), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis)
- inflammation of the liver
- skin colour change in patches (vitiligo), redness of the skin, unusual hair loss or thinning, hives (itchy, bumpy rash), dry skin
- inflammation of the joints (arthritis), muscle spasm, muscle weakness
- kidney failure (including abrupt loss of kidney function)
- pain, chest pain, chills

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)
- decrease in neutrophils with fever
- acid in the blood produced from diabetes (diabetic ketoacidosis)
- increased acid levels in the blood
- inflammation of the brain; 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)
- inflammation of the eye which causes redness or pain
- irregular or abnormal heart beat, inflammation of the heart muscle, slow heart rate
- inflammation of the duodenum
- 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), severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (other lichen disorders)
- aching muscles, muscle tenderness of weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)
- inflammation of the kidney

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

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
- temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome), 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)
- bowel perforation,
- 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), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- 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), loosening of membrane at the back of the eye (serous retinal detachment)
- 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 pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- 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)
- inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis). Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems

Changes in test results
YERVOY 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

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 YERVOY

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 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 YERVOY contains

- The active substance is ipilimumab.
  Each ml of concentrate contains 5 mg of ipilimumab.
  Each 10 ml vial contains 50 mg of ipilimumab.
  Each 40 ml vial contains 200 mg of ipilimumab.

- The other ingredients are Tris-hydrochloride, sodium chloride (see section 2 "YERVOY contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What YERVOY looks like and contents of the pack
YERVOY concentrate for solution for infusion is clear to slightly opalescent, colourless to pale yellow and may contain light (few) particulates.

It is available in packs containing either 1 glass vial of 10 ml or 1 glass vial of 40 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
CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
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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 should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose:
Ipilimumab monotherapy or ipilimumab in combination with nivolumab:
The **prescribed dose** for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of YERVOY concentrate may be needed to give the total dose for the patient.

- Each 10 ml vial of YERVOY concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab.
- The **total ipilimumab dose** in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The **volume of YERVOY concentrate** to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Preparing the infusion:
Take care to ensure aseptic handling when you prepare the infusion.

YERVOY can be used for intravenous administration either:
- **without dilution**, after transfer to an infusion container using an appropriate sterile syringe; or
- **after diluting** to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the YERVOY concentrate, you can use either:
  - sodium chloride 9 mg/ml (0.9%) solution for injection; or
  - 50 mg/ml (5%) glucose solution for injection

STEP 1
- Allow the appropriate number of vials of YERVOY to stand at room temperature for approximately 5 minutes.
- Inspect the YERVOY concentrate for particulate matter or discoloration. YERVOY concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of YERVOY concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).
- 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.

Administration:
The YERVOY infusion must not be administered as an intravenous push or bolus injection.
Administer the YERVOY infusion intravenously **over a period of 30 minutes**.

The YERVOY 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).

The YERVOY infusion is compatible with:
- PVC infusion sets
- Polyethersulfone (0.2 µm to 1.2 µm) and nylon (0.2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion.

Storage conditions and shelf life:

Unopened vial
YERVOY 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. YERVOY should not be frozen.

Do not use YERVOY after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

YERVOY infusion
From a microbiological point of view, once opened, the medicine **should be infused or diluted and infused immediately**. The chemical and physical in-use stability of the undiluted or diluted infusion solution (between 1 and 4 mg/ml) has been demonstrated for 24 hours at room temperature (20°C to 25°C) or when refrigerated (2°C to 8°C). If not used immediately, the infusion solution (undiluted or diluted) must be used within 24 hours when stored either under refrigeration (2°C to 8°C) or at room temperature (20°C to 25°C). Other in-use storage time and conditions are the responsibility of the user.

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.

Table 1: EU 添付文書の概要

国名	EU
販売名	YERVOY 5 mg/ml concentrate for solution for infusion
会社名	Bristol Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland
一般的名称	イピリムマブ
承認年月日	2011 年 7 月 13 日
剤型・含量	点滴静注用濃縮液（無菌濃縮液） 濃縮液 1 mL 中にイピリムマブ 5 mg を含有する。 10 mL バイアルはイピリムマブ 50 mg を含有する。 40 mL バイアルはイピリムマブ 200 mg を含有する。 イピリム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から産生される完全ヒト型抗 CTLA-4 モノクローナル抗体（IgG1κ）である。
効能・効果	**黒色腫** YERVOY の単剤療法又はニボルマブとの併用療法は、成人及び 12 歳以上の青年期における進行性（切除不能又は転移性）悪性黒色腫の治療を適応とする（4.4 項参照）。 ニボルマブ単剤療法と比較して、ニボルマブとイピリムマブの併用療法による無増悪生存期間（PFS）及び全生存期間（OS）の延長は、腫瘍 PD-L1 発現量が低い患者においてのみ確立されている（4.4 項及び 5.1 項参照）。 **腎細胞癌（RCC）** YERVOY とニボルマブの併用療法は、intermediate 又は poor リスクの成人進行性腎細胞癌患者の一次治療を適応とする（5.1 項参照）。 **非小細胞肺癌（NSCLC）** YERVOY は、ニボルマブ及び 2 サイクルのプラチナ製剤ベースの化学療法との併用で、EGFR 遺伝子変異又は ALK 転座のない成人転移性非小細胞肺癌の一次治療を適応とする。 **悪性胸膜中皮腫（MPM）** YERVOY とニボルマブの併用療法は、切除不能な悪性胸膜中皮腫の成人患者の一次治療を適応とする。 **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・直腸癌（CRC）** YERVOY とニボルマブの併用療法は、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・直腸癌の成人患者に対して、以下の適応とする。 - 切除不能又は転移性結腸・直腸癌の一次治療 - フッ化ピリミジン系薬剤を含む多剤併用化学療法後の転移性結腸・直腸癌の治療（5.1 項参照）。

	<u>食道扁平上皮癌（OSCC）</u> YERVOY とニボルマブの併用療法は、腫瘍細胞の PD-L1 発現が 1%以上の切除不能な進行、再発又は転移性食道扁平上皮癌の成人患者の一次治療を適応とする。 **<u>肝細胞癌（HCC）</u>** YERVOY とニボルマブの併用療法は、切除不能又は進行した肝細胞癌の成人患者に対する一次治療を適応とする。
用法・用量	*YERVOY 単剤療法* *黒色腫* *成人及び 12 歳以上の青年* YERVOY の推奨導入レジメンは、3 週間ごとに 3 mg/kg を 30 分かけて計 4 回静脈内投与することである。新病変の出現又は既存病変の増大にかかわらず、忍容性に応じて寛解導入療法の全レジメン（4 回投与）を実施する。腫瘍縮小効果の評価は、寛解導入療法完了後にのみ実施する。 *YERVOY とニボルマブの併用* *黒色腫* 12 歳以上で体重 50 kg 以上の成人及び青年において、ニボルマブ 1 mg/kg との併用でイピリムマブ 3 mg/kg を最初の 4 回は 3 週間間隔で静脈内投与する。その後、表 1 に示すように、ニボルマブの単剤療法期としてニボルマブ 240 mg を 2 週間間隔**又は** 480 mg を 4 週間間隔で静脈内投与する（5.1 項及び 5.2 項参照）。ニボルマブ単剤療法期の初回投与は、以下の時点で行う。 • ニボルマブとイピリムマブの併用療法で 240 mg を 2 週間間隔で使用している場合は、ニボルマブとイピリムマブの併用の最終投与から 3 週間後、又は • ニボルマブとイピリムマブの併用療法で 480 mg を 4 週間間隔で使用している場合は、ニボルマブとイピリムマブの併用療法の最終投与から 6 週間後。 12 歳以上で体重 50 kg 未満の青年には、最初の 4 回はイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を 3 週間間隔で静脈内投与する。その後、表 1 に示すように、ニボルマブの単剤療法期としてニボルマブ 3 mg/kg を 2 週間間隔**又は** 6 mg/kg を 4 週間間隔で静脈内投与する（5.1 項及び 5.2 項参照）。ニボルマブ単剤療法期の初回投与は、以下の時点で行う。 • 3 mg/kg を 2 週間間隔で使用する場合は、ニボルマブとイピリムマブ併用の最終投与から 3 週間後、**又は** • 6 mg/kg を 4 週間間隔で使用している場合は、ニボルマブとイピリムマブ併用の最終投与から 6 週間後。

表 1: イピリムマブとニボルマブ併用時の静脈内投与の推奨用量及び投与時間

	併用療法期: 3 週間ごとに 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，体重 50 kg 以上）: 240 mg を 2 週間間隔で 30 分かけて投与、又は 480 mg を 4 週間間隔で 60 分かけて投与 青年（12 歳以上，体重 50 kg 未満）: 3 mg/kg を 2 週間間隔で 30 分かけて投与、又は 6 mg/kg を 4 週間間隔で 60 分かけて投与
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	-

腎細胞癌

推奨用量は、イピリムマブ 1 mg/kg とニボルマブ 3 mg/kg を最初の 4 回は 3 週間間隔で静脈内投与する。その後、表 2 に示すように、ニボルマブの単剤療法期として 240 mg を 2 週間間隔**又は** 480 mg を 4 週間間隔で静脈内投与する。ニボルマブ単剤療法期の初回投与は、以下の時点で行う。

- ニボルマブとイピリムマブの併用療法で 240 mg を 2 週間間隔で使用している場合は、ニボルマブとイピリムマブの併用の最終投与から 3 週間後、又は
- ニボルマブとイピリムマブの併用療法で 480 mg を 4 週間間隔で使用している場合は、ニボルマブとイピリムマブの併用療法の最終投与から 6 週間後。

表 2: RCC に対するニボルマブ併用下でのイピリムマブ静脈内投与の推奨用量及び投与時間

	併用療法期: 3 週間ごとに 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 分かけて投与、又は 480 mg を 4 週間間隔で 60 分かけて投与
イピリムマブ	1 mg/kg を 30 分かけて投与	-

dMMR 又は MSI-H 結腸・直腸癌

dMMR 又は MSI-H の CRC に対する一次治療の推奨用量は、イピリムマブ 1 mg/kg とニボルマブ 240 mg を 3 週間間隔で最大 4 回静脈内投与し、その後、ニボルマブ単剤を表 3 に示すように 240 mg を 2 週間間隔**又は** 480 mg を 4 週間間隔で静脈内投与する。ニボルマブ単剤療法期の初回投与は、ニボルマブとイピリムマブの併用療法の最終投与から 3 週間後に行う。ニボルマブの投与は、病勢進行もしくは許容できない毒性が認められるまで、又は病勢進行が認められない患者では最長 24 ヵ月まで継続することが推奨される。

dMMR 又は MSI-H CRC に対してフッ化ピリミジン系薬剤を含む多剤併用化学療法による治療歴を有する患者に対する推奨用量は、表 3 に示すとおり、イピリムマブ 1 mg/kg とニボルマブ 3 mg/kg を併用し、最初の 4 回は 3 週間間隔で静脈内投与し、その後はニボルマブ単剤療法として 240 mg を 2 週間間隔で静脈内投与する。単剤療法期では、イピリムマブとニボルマブの併用療法の最終投与から 3 週間後にニボルマブの初回投与を行う。

表 3: dMMR 又は MSI-H を有する CRC に対するニボルマブ併用下でのイピリムマブ静脈内投与の推奨用量及び注入時間

		併用療法期: 3 週間ごとに 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 分かけて投与、又は 480 mg を 4 週間間隔で 30 分かけて投与
	フッ化ピリミジン系薬剤を含む多剤併用化学療法による前治療後	3 mg/kg を 30 分かけて投与	240 mg を 2 週間間隔で 30 分かけて投与
イピリムマブ		1 mg/kg を 30 分かけて投与	-

悪性胸膜中皮腫

推奨用量はイピリムマブ 1 mg/kg を 6 週間間隔で 30 分かけて静脈内投与するとともに、ニボルマブ 360 mg を 3 週間間隔で 30 分かけて静脈内投与する。疾患進行が認められない患者では最長 24 ヵ月間投与を継続する。

食道扁平上皮癌

推奨用量は、イピリムマブ 1 mg/kg を 6 週間間隔で 30 分かけて静脈内投与するとともに、ニボルマブ 3 mg/kg を 2 週間間隔又はニボルマブ 360 mg を 3 週間間隔で 30 分かけて静脈内投与する。疾患進行又は許容できない毒性が認められるまで、又は疾患進行が認められない患者では最長 24 ヵ月まで投与することが推奨される。

肝細胞癌

推奨用量は、イピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併用し、3 週間間隔で 4 回まで静脈内投与する。その後、表 4 に示すとおり、ニボルマブ単剤療法として 240 mg を 2 週間間隔、又は 480 mg を 4 週間間隔で静脈内投与する（5.1 項及び 5.2 項参照）。投与は、病勢進行もしくは許容できない毒性が認められるまで、又は最長 24 ヵ月まで継続することが推奨される。ニボルマブ単剤療法期の初回投与は、以下の時点で行う：

- 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において、ニボルマブとイピリムマブの併用の最終投与から 3 週間後。

表 4: HCC に対するニボルマブ併用下でのイピリムマブ静脈内投与の推奨用量及び注入時間

	併用療法期: 3 週間ごとに 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 分かけて投与、又は 480 mg を 4 週間間隔で 30 分かけて投与
イピリムマブ	3 mg/kg を 30 分かけて投与	-

YERVOY とニボルマブ及び化学療法の併用

非小細胞肺癌

推奨用量は、イピリムマブ 1 mg/kg を 6 週間間隔で 30 分かけて静脈内投与するとともに、ニボルマブ 360 mg を 3 週間間隔で 30 分かけて静脈内投与し、プラチナ製剤を含む化学療法を 3 週間間隔で投与する。2 サイクルの化学療法終了後、ニボルマブ 360 mg を 3 週間間隔で静脈内投与するのと併用して、イピリムマブ 1 mg/kg を 6 週間間隔で投与を継続する。疾患進行又は許容できない毒性が認められるまで、又は疾患進行が認められない患者では最長 24 ヵ月まで投与することが推奨される。

投与期間

YERVOY とニボルマブの併用療法は、臨床上の有益性が認められる限り、又は患者が治療に耐えられなくなるまで（適応症に規定されている場合は最長治療期間まで）継続すること。

非典型的な反応（すなわち、最初の数ヵ月以内に最初の一過性の腫瘍サイズの増大又は小さな新病変が認められ、その後腫瘍が縮小した場合）が認められている。臨床的に安定している患者では、最初に疾患進行のエビデンスが認められても、疾患進行が確認されるまで YERVOY とニボルマブの併用療法を継続することが推奨される。

ベースライン時及び YERVOY の各投与前に肝機能検査（LFT）及び甲状腺機能検査を評価すること。さらに、YERVOY の投与期間中は、下痢及び大腸炎を含む免疫に関連した副作用の徴候又は症状を評価しなければならない（表 5A、表 5B 及び 4.4 項参照）。

投与の永続的中止又は投与中断

免疫に関連した副作用の管理には、YERVOY の投与中断又は投与中止及び高用量コルチコステロイドの全身投与の開始が必要となる場合がある。場合によっては、他の免疫抑制療法の追加を検討してもよい（4.4 項参照）。

増量又は減量は推奨されない。個々の安全性及び忍容性に基づき、投与延期又は投与中止が必要となる場合がある。

投与の永続的な中止又は中断に関するガイドラインを、YERVOY 単剤療法については表 5A 及び表 5B に、YERVOY とニボルマブとの併用療法又は併用療法後の次治療

（ニボルマブ単剤療法）については表 5C に示す。免疫に関連した副作用の管理に関する詳細なガイドラインを 4.4 項に示す。

表 5A: YERVOY 単剤療法の永続的な中止時期

次の副作用があらわれた場合は、投与を中止すること。これらの副作用の管理には、免疫に関連することが示された又は疑われる場合、高用量コルチコステロイドの全身投与も必要となる場合がある（詳細な管理ガイドラインについては 4.4 項を参照）。

副作用	NCI-CTCAE v 4 グレード[a]
消化器: 重度の症状（腹痛、重度の下痢又は排便回数の著明な変化、血便、消化管出血、消化管穿孔）	• グレード 3 又は 4 の下痢又は大腸炎
肝臓: アスパラギン酸アミノトランスフェラーゼ（AST）、アラニンアミノトランスフェラーゼ（ALT）又は総ビリルビンの重度の増加又は肝毒性の症状	• グレード 3 又は 4 の AST、ALT 又は総ビリルビン増加
皮膚: 生命を脅かす皮疹（スティーヴンス・ジョンソン症候群又は中毒性表皮壊死融解症を含む）又は日常生活動作を妨げる又は医学的介入を必要とする重度の広範なそう痒症	• グレード 4 の発疹又はグレード 3 のそう痒症
神経: 重度の運動又は感覚ニューロパチーの新規発現又は悪化	• グレード 3 又は 4 の運動又は感覚ニューロパチー
その他の器官系[b]: （例: 腎炎、肺臓炎、膵炎、非感染性心筋炎、糖尿病）	• グレード 3 以上の免疫に関連した反応[c] • 局所免疫抑制療法に反応しないグレード 2 以上の免疫に関連した眼障害 • グレード 4 の糖尿病

[a] 毒性グレードは米国国立がん研究所の有害事象共通用語規準に従う。第 4.0 版（NCI-CTCAE v4）。

[b] 免疫に関連することが示された又は疑われるその他の副作用は、CTCAE に従ってグレードを評価する。YERVOY を中止するかどうかは重症度に基づいて決定すること。

[c] ホルモン補充療法でコントロールされている重度（グレード 3 又は 4）の内分泌障害を有する患者は治療を継続してもよい。

表 5B: YERVOY 単剤療法の休薬時期

次の免疫に関連した副作用が認められた場合は、YERVOY を休薬する[a]。詳細な管理ガイドラインについては 4.4 項を参照のこと。	
副作用	措置
消化器: 内科的治療でコントロール不能、持続（5～7 日間）、又は再発する中等度の下痢又は大腸炎	1 副作用がグレード 1 又は 0 に回復する（又はベースライン値に回復する）まで、本剤を休薬する。 2 回復した場合、投与を再開する。[d] 3 未回復の場合は回復するまで休薬を継続し、回復後に投与を再開する。[d] 4 グレード 1 又は 0 への回復又はベースラインへの回復が認められない場合は、YERVOY の投与を中止する。
肝臓: グレード 2 の AST、ALT 又は総ビリルビン増加	
皮膚: 病因を問わない中等度から重度（グレード 3）[b] の皮疹又は広範囲/強度（グレード 2）のそう痒症	
内分泌: ホルモン補充療法又は高用量免疫抑制療法で十分にコントロールできない下垂体炎及び甲状腺炎などの内分泌腺の重度の副作用 グレード 3 の糖尿病	
神経: 中等度（グレード 2）[b] の原因不明の運動ニューロパチー、筋力低下、又は感覚ニューロパチー（4 日間を超えて持続）	
その他の中等度の副作用[c]	

[a] YERVOY の減量は推奨されない。
[b] 毒性グレードは米国国立がん研究所の有害事象共通用語規準に従う。第 4.0 版（NCI-CTCAE v4）。
[c] 免疫に関連すると考えられるその他の器官系の副作用は、CTCAE に従ってグレード分類する。投与を中断するかどうかは重症度に基づいて決定する。
[d] 4 回すべての投与又は初回投与から 16 週後のいずれか早い時点まで。

表 5C: YERVOY とニボルマブとの併用療法又は併用療法後の次治療（ニボルマブ単剤療法）で推奨される治療変更

免疫に関連した副作用	重症度	治療の変更
免疫に関連した肺臓炎	グレード 2 の肺臓炎	症状が消失し、X 線画像上の異常が改善し、コルチコステロイドによる管理が完了するまで投与を中断する
	グレード 3 又は 4 の肺臓炎	投与を中止する
免疫に関連した大腸炎	グレード 2 の下痢又は大腸炎	症状が消失し、必要に応じてコルチコステロイドによる管理が完了するまで、投与を中断する
	グレード 3 又は 4 の下痢又は大腸炎	投与を中止する

	HCC を伴わない免疫に関連した肝炎	グレード 2 のアスパラギン酸アミノトランスフェラーゼ（AST）、アラニンアミノトランスフェラーゼ（ALT）又は総ビリルビンの増加	臨床検査値がベースライン値に回復し、必要に応じてコルチコステロイドによる管理が完了するまで、投与を中断する
		グレード 3 又は 4 の AST、ALT 又は総ビリルビン増加	投与を中止する
	HCC を伴う免疫に関連した肝炎	ベースラインで AST/ALT が正常範囲内にあり、ULN の 3 倍超 10 倍以下に増加 又は ベースラインの AST/ALT が ULN の 1 倍超 3 倍以下、かつ ULN の 5 倍超 10 倍以下に増加 又は ベースラインの AST/ALT が ULN の 3 倍超 5 倍以下、かつ ULN の 8 倍超 10 倍以下に増加	臨床検査値がベースライン値に回復し、必要に応じてコルチコステロイドによる管理が完了するまで、投与を中断する
		AST/ALT が ULN の 10 倍超 又は 総ビリルビンが ULN の 3 倍超	投与を中止する
	免疫に関連した腎炎及び腎機能障害	グレード 2 又は 3 のクレアチニン増加	クレアチニンがベースライン値に回復し、コルチコステロイドによる管理が完了するまで投与を中断する
		グレード 4 のクレアチニン増加	投与を中止する
	免疫に関連した内分泌障害	症候性のグレード 2 又は 3 の甲状腺機能低下症、甲状腺機能亢進症、下垂体炎、 グレード 2 の副腎機能不全 グレード 3 の糖尿病	症状が消失し、コルチコステロイド（急性炎症の症状に必要な場合）による管理が完了するまで投与を中断する。症状が認められない限り、ホルモン補充療法[a]の下で投与を継続する。
		グレード 4 の甲状腺機能低下症 グレード 4 の甲状腺機能亢進症 グレード 4 の下垂体炎 グレード 3 又は 4 の副腎機能不全 グレード 4 の糖尿病	投与を中止する
	免疫に関連した皮膚副作用	グレード 3 の発疹	症状が消失し、コルチコステロイドによる管理が完了するまで投与を中断する
		グレード 4 の発疹	投与を中止する
		スティーヴンス・ジョンソン症候群（SJS）又は中毒性表皮壊死融解症（TEN）	投与を中止する（4.4 項参照）

<table>
<tr><td></td><td>
<table>
<tr><td>免疫に関連した心筋炎</td><td>グレード 2 の心筋炎</td><td>症状が消失し、コルチコステロイドによる管理が完了するまで投与を中断する [b]</td></tr>
<tr><td></td><td>グレード 3 又は 4 の心筋炎</td><td>投与を中止する</td></tr>
<tr><td>その他の免疫に関連した副作用</td><td>グレード 3（初発）</td><td>投与を中断する</td></tr>
<tr><td></td><td>グレード 4 又はグレード 3 の再発、治療変更にもかかわらずグレード 2 又は 3 が持続、コルチコステロイドをプレドニゾン換算で 10 mg/日まで減量できない</td><td>投与を中止する</td></tr>
</table>
Note: 毒性グレードは米国国立がん研究所の有害事象共通用語規準第 4.0 版（NCI-CTCAE v4）に従う。
[a] ホルモン補充療法の使用に関する推奨事項を 4.4 項に示す。
[b] 免疫に関連した心筋炎の既往を有する患者にイピリムマブとニボルマブの併用療法を再開した場合の安全性は不明である。

以下の場合は、YERVOY とニボルマブの併用療法を永続的に中止すること。
• グレード 4 又は再発性のグレード 3 の副作用
• 管理にもかかわらず持続するグレード 2 又は 3 の副作用

YERVOY とニボルマブを併用する場合、いずれかの薬剤を休薬した場合は、もう一方の薬剤も休薬すること。投与延期後に投与を再開する場合、個々の患者の評価に基づき、併用療法又はニボルマブ単剤療法のいずれかを再開することができる。</td></tr>
<tr><td>禁忌</td><td>本剤の有効成分又は 6.1 項に記載されている添加剤のいずれかに対する過敏症。</td></tr>
<tr><td>警告及び使用上の注意</td><td><u>イピリムマブとニボルマブの併用</u>
イピリムマブを併用投与する場合、投与開始前に他の併用療法の SmPC を参照すること。ニボルマブの投与に関連する警告及び使用上の注意の詳細については、ニボルマブの SmPC を参照のこと。ほとんどの免疫に関連した副作用は、コルチコステロイドの開始及び治療の変更（4.2 項参照）を含む適切な管理により改善又は消失した。ニボルマブとイピリムマブとの併用療法では、ニボルマブの単剤療法と比較して、免疫に関連した副作用の発現頻度が高かった。

併用療法では、肺塞栓症を含む心臓及び肺の有害事象も報告されている。投与前及び投与中は定期的に、心臓及び肺の副作用、並びに電解質障害及び脱水を示唆する臨床徴候、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こと。生命を脅かす又は再発性の重度の心臓及び肺の副作用が発現した場合は、イピリムマブとニボルマブの併用療法を中止すること（4.2 項参照）。

イピリムマブとニボルマブの併用療法では、治療中又は治療中止後のいずれかの時点で副作用が発現する可能性があるため、継続的に（少なくとも最終投与後 5 ヵ月まで）患者を観察すること。</td></tr>
</table>

	免疫に関連した反応 イピリムマブは、その作用機序に関連するものと考えられる免疫活性の亢進、又は過剰に起因する炎症性の副作用（免疫に関連した副作用）を伴う。免疫に関連した副作用は、重度又は生命を脅かす可能性があり、消化管、肝臓、皮膚、神経系、内分泌系、又はその他の器官系に生じる可能性がある。ほとんどの免疫に関連した副作用は導入期に発現したが、イピリムマブの最終投与から数ヵ月後に発現した例も報告されている。他の原因が特定されない限り、下痢、排便回数増加、血便、肝機能検査値の増加、発疹及び内分泌障害は炎症性でイピリムマブに関連すると判断しなければならない。生命を脅かす合併症を最小限に抑えるためには、早期診断と適切な管理が不可欠である。 重度の免疫に関連した副作用の管理には、追加の免疫抑制療法の有無にかかわらず、高用量コルチコステロイドの全身投与が必要となる場合がある。 イピリムマブの単剤療法及びニボルマブとの併用療法における、免疫に関連した副作用の管理ガイドラインを以下に示す。 免疫に関連した副作用が疑われる場合は、病因を確認するか、他の原因を除外するために適切な評価を行う。副作用の重症度に応じて、イピリムマブの投与又はイピリムマブとニボルマブの併用療法は中断し、コルチコステロイドを投与する。併用療法の結果として発現した副作用を治療するためにコルチコステロイドによる免疫抑制剤を使用する場合は、改善が認められた時点で 1 ヵ月以上かけて漸減を開始する。急激な漸減は副作用の悪化又は再発を招くおそれがある。コルチコステロイドの使用にもかかわらず悪化又は改善が認められない場合は、コルチコステロイド以外の免疫抑制療法を追加する。 患者が免疫抑制用量のコルチコステロイド又はその他の免疫抑制療法を受けている間は、イピリムマブとニボルマブの併用療法を再開しないこと。免疫抑制療法を受けている患者では、日和見感染を予防するために抗生物質を予防的に使用すること。 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は、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。 免疫に関連した消化管反応 *イピリムマブ単剤療法* イピリムマブは重篤な免疫に関連した消化管反応を伴う。臨床試験において消化管穿孔による死亡例が報告されている（4.8 項参照）。 進行性（切除不能又は転移性）悪性黒色腫の第 3 相試験（MDX010-20、第 5.1 項を参照）において患者にイピリムマブ 3 mg/kg を単剤投与したとき、重度又は致死性（グレード 3～5）の免疫に関連した消化管反応の発現までの期間の中央値は投与開始から 8 週間（範囲: 5～13 週間）であった。治験実施計画書に規定した管理ガイドラインにより、ほとんどの症例（90%）で回復（軽度［グレード 1］以下又はベースライン時の重症度への改善と定義）が認められ、発現から回復までの期間の中央値は 4 週間（範囲: 0.6～22 週間）であった。

	免疫に関連した大腸炎又は消化管穿孔を示唆する可能性のある消化管の徴候及び症状について、患者をモニタリングしなければならない。臨床症状には下痢、排便回数増加、腹痛、血便排泄などがあり、発熱を伴う場合と伴わない場合がある。臨床試験では、免疫に関連した大腸炎は粘膜の炎症（潰瘍の有無を問わない）並びにリンパ球及び好中球の浸潤を伴っていた。コルチコステロイド抵抗性の免疫に関連した大腸炎患者において、サイトメガロウイルス（CMV）感染/再活性化の市販後症例が報告されている。下痢又は大腸炎が認められた場合は、感染性又はその他の病因を除外するため、便感染症の精密検査を実施する。 下痢又は大腸炎の管理に関する推奨事項は、症状の重症度（NCI-CTCAE v4 の重症度分類に基づく）に基づく。軽度から中等度（グレード 1 又は 2）の下痢（6 回/日までの排便回数増加）又は軽度から中等度の大腸炎（例: 腹痛又は血便）が疑われる場合は、イピリムマブの投与を継続してもよい。対症療法（例: ロペラミド、補液）及び綿密なモニタリングが推奨される。軽度から中等度の症状が再発した場合、又は 5～7 日間持続した場合は、予定されたイピリムマブの投与を中断し、コルチコステロイド療法（例: プレドニゾン 1 mg/kg を 1 日 1 回経口投与、又は同等の薬剤）を開始する。グレード 0～1 まで回復又はベースライン値まで回復した場合、イピリムマブの投与を再開してもよい（4.2 項参照）。 重度（グレード 3 又は 4）の下痢又は大腸炎（4.2 項参照）が認められた患者では、イピリムマブの投与を永続的に中止しなければならず、高用量コルチコステロイドの静脈内投与による全身療法を直ちに開始しなければならない。（臨床試験では、メチルプレドニゾロン 2 mg/kg/日が使用された）。下痢及びその他の症状がコントロール良好になったら、臨床的判断に基づいてコルチコステロイドの漸減を開始する。臨床試験では、急速な漸減（1 ヵ月未満）により、一部の患者で下痢又は大腸炎が再発した。消化管穿孔又は腹膜炎の徴候について患者を評価しなければならない。 コルチコステロイド抵抗性の下痢又は大腸炎の管理に関する臨床試験の経験は限られている。コルチコステロイド抵抗性の免疫に関連した大腸炎では、他の原因が除外された場合（生検でウイルス PCR により評価したサイトメガロウイルス［CMV］感染/再活性化、並びにその他のウイルス性、細菌性及び寄生虫性の病因を含む）、コルチコステロイドのレジメンに別の免疫抑制剤の追加を検討すること。臨床試験では、禁忌でない限り、インフリキシマブ 5 mg/kg の単回投与を追加した。消化管穿孔又は敗血症が疑われる場合は、インフリキシマブを使用してはならない（インフリキシマブの SmPC を参照）。 <u>免疫に関連した大腸炎</u> *イピリムマブとニボルマブの併用* イピリムマブとニボルマブの併用療法において、重度の下痢又は大腸炎が認められている（4.8 項参照）。下痢及び腹痛、粘液便又は血便などの大腸炎の追加症状について、患者をモニタリングすること。感染及び疾患に関連した原因を除外する必要がある。 グレード 4 の下痢又は大腸炎が発現した場合は、イピリムマブとニボルマブの併用療法を永続的に中止し、メチルプレドニゾロン換算で 1～2 mg/kg/日の用量でコルチコステロイドの投与を開始すること。

イピリムマブとニボルマブの併用療法で認められたグレード 3 の下痢又は大腸炎は、投与を永続的に中止し、メチルプレドニゾロン換算で 1～2 mg/kg/日の用量でコルチコステロイドの投与を開始する必要がある。

グレード 2 の下痢又は大腸炎が発現した場合は、イピリムマブとニボルマブの併用療法を中断する。持続性の下痢又は大腸炎は、メチルプレドニゾロン換算で 0.5～1 mg/kg/日のコルチコステロイドで管理する。改善が認められた場合、必要に応じてコルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法を再開することができる。コルチコステロイドの投与開始にもかかわらず悪化又は改善が認められない場合は、コルチコステロイドをメチルプレドニゾロン換算で 1～2 mg/kg/日に増量し、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。

<u>免疫に関連した肺臓炎</u>

イピリムマブとニボルマブの併用

イピリムマブとニボルマブの併用療法では、死亡例を含む重度の肺臓炎又は間質性肺疾患が認められている（4.8 項参照）。X 線画像上の変化（例: 限局性のすりガラス陰影、斑状の濾液）、呼吸困難及び低酸素症などの肺臓炎の徴候及び症状について患者をモニタリングすること。感染及び疾患に関連した原因を除外すること。

グレード 3 又は 4 の肺臓炎の場合、イピリムマブとニボルマブの併用療法は永続的に中止しなければならず、コルチコステロイドはメチルプレドニゾロン換算で 2～4 mg/kg/日の用量で開始する。

グレード 2（症候性）の肺臓炎の場合、イピリムマブとニボルマブの併用療法は中断し、メチルプレドニゾロン換算で 1 mg/kg/日の用量でコルチコステロイドの投与を開始する。改善が認められた場合、コルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法を再開することができる。コルチコステロイドの投与開始にもかかわらず悪化又は改善が認められない場合、コルチコステロイドの用量をメチルプレドニゾロン換算で 2～4 mg/kg/日に増量し、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。

<u>免疫に関連した肝毒性</u>

イピリムマブ単剤療法

イピリムマブは重篤な免疫に関連した肝毒性を伴う。致死的な肝不全が臨床試験で報告されている（4.8 項参照）。

MDX010-20 試験でイピリムマブ 3 mg/kg を単剤投与した患者において、中等度から重度又は致死的（グレード 2～5）の免疫に関連した肝毒性が発現するまでの期間は、投与開始から 3～9 週間であった。治験実施計画書に規定された管理ガイドラインによる回復までの期間は、0.7～2 週間であった。

早期の臨床検査値の変化は免疫に関連した肝炎の兆候を示唆する可能性があるため、イピリムマブの各投与前に肝トランスアミナーゼ及びビリルビンを評価しなければな

らない（4.2 項参照）。臨床症状を伴わずに肝機能検査値が増加することがある。AST 及び ALT 又は総ビリルビンの増加は、感染症、腫瘍進行又は併用薬など他の肝障害の原因を除外するために評価し、回復するまでモニタリングする。免疫に関連した肝毒性を発現した患者の肝生検では、急性炎症のエビデンス（好中球、リンパ球、マクロファージ）が認められた。

グレード 2 のトランスアミナーゼ又は総ビリルビン増加が認められた患者では、予定されたイピリムマブの投与を中断し、回復するまで肝機能検査値をモニタリングしなければならない。改善した場合、イピリムマブの投与を再開してもよい（4.2 項参照）。

グレード 3 又は 4 のトランスアミナーゼ又は総ビリルビン増加が認められた患者では、投与を永続的に中止し（4.2 項参照）、高用量コルチコステロイドの全身静脈内投与療法（例: メチルプレドニゾロン 2 mg/kg/日又は同等品）を直ちに開始しなければならない。このような患者では、正常化するまで肝機能検査値をモニタリングしなければならない。症状が消失し、肝機能検査値が持続的に改善又はベースライン値に回復した場合、臨床的判断に基づいてコルチコステロイドの漸減を開始する。漸減は 1 ヵ月以上かけて行う。漸減中の肝機能検査値の増加は、コルチコステロイドの用量を増量し、漸減を緩徐に行うことで管理可能である。

コルチコステロイド療法に抵抗性を示す重大な肝機能検査値増加が認められた患者については、コルチコステロイド療法に別の免疫抑制剤の追加を検討してもよい。臨床試験では、コルチコステロイド療法に反応しない患者、又はコルチコステロイド漸減中に肝機能検査値増加が認められ、コルチコステロイドの増量に反応しない患者に、ミコフェノール酸　モフェチルを投与した（ミコフェノール酸　モフェチルの SmPC を参照）。

イピリムマブとニボルマブの併用

イピリムマブとニボルマブの併用療法で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について患者をモニタリングすること。感染及び疾患に関連した原因を除外すること。

グレード 3 又は 4 のトランスアミナーゼ又は総ビリルビン増加が認められた場合は、イピリムマブとニボルマブの併用療法を永続的に中止し、メチルプレドニゾロン換算で 1～2 mg/kg/日の用量でコルチコステロイドの投与を開始する。

グレード 2 のトランスアミナーゼ又は総ビリルビン増加が認められた場合は、イピリムマブとニボルマブの併用療法を中断する。これらの臨床検査値の増加が持続する場合は、メチルプレドニゾロン換算で 0.5～1 mg/kg/日のコルチコステロイドで管理する。改善が認められた場合、必要に応じてコルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法を再開することができる。コルチコステロイドの投与開始にもかかわらず悪化又は改善が認められない場合は、コルチコステロイドをメチルプレドニゾロン換算で 1～2 mg/kg/日に増量し、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。

	免疫に関連した皮膚の副作用 過去のがん免疫刺激療法において、重度又は生命を脅かす皮膚の副作用が発現したことがある患者に、イピリムマブの投与又はイピリムマブとニボルマブの併用療法を検討する場合は注意が必要である。 *イピリムマブ単剤療法* イピリムマブは、免疫に関連すると考えられる重度の皮膚の副作用を伴う。中毒性表皮壊死融解症（TEN）（スティーヴンス・ジョンソン症候群を含む）の症例が稀に認められており、一部は死亡に至っている。臨床試験及び市販後使用において、好酸球増加と全身症状を伴う薬物反応（DRESS）の稀な症例も報告されている（4.8 項参照）。 DRESS は、発熱、リンパ節腫脹、顔面浮腫及び内臓病変（肝臓、腎臓、肺）のうち 1 つ以上を有する好酸球増加症を伴う発疹として発現する。DRESS は、医薬品曝露から発症までの潜伏期間が長い（2～8 週間）ことが特徴である。 イピリムマブにより誘発された発疹及びそう痒症は、主に軽度又は中等度（グレード 1 又は 2）であり、対症療法に反応した。MDX010-20 試験でイピリムマブ 3 mg/kg 単剤療法を受けた患者では、中等度から重度又は致死的（グレード 2～5）な皮膚の副作用の発現までの期間の中央値は、投与開始から 3 週間（範囲: 0.9～16 週間）であった。治験実施計画書に規定された管理ガイドラインにより、ほとんどの症例（87%）で回復が認められ、発現から回復までの期間の中央値は 5 週間（範囲: 0.6～29 週間）であった。 イピリムマブによる発疹及びそう痒症は、重症度に基づいて管理すること。軽度から中等度（グレード 1 又は 2）の発疹が認められた患者は、対症療法（抗ヒスタミン薬など）を行いながらイピリムマブの投与を継続してもよい。軽度から中等度の発疹又は軽度のそう痒症が 1～2 週間持続し、コルチコステロイド外用剤で改善しない場合は、経口コルチコステロイド療法を開始する（例: プレドニゾン 1 mg/kg1 日 1 回又は同等品）。 重度（グレード 3）の発疹が認められた患者では、予定されたイピリムマブの投与を中断する。初期症状が軽度（グレード 1）に改善又は消失した場合、イピリムマブの投与を再開することができる（4.2 項参照）。 極めて重度（グレード 4）の発疹又は重度（グレード 3）のそう痒症（4.2 項参照）が認められた患者では、イピリムマブの投与を永続的に中止しなければならず、高用量のコルチコステロイドの静脈内投与（例: メチルプレドニゾロン 2 mg/kg/日）を直ちに開始すること。発疹又はそう痒症がコントロール良好になったら、臨床的判断に基づいてコルチコステロイドの漸減を開始する。漸減は 1 ヵ月以上かけて行う。 *イピリムマブとニボルマブの併用* イピリムマブとニボルマブの併用療法で、重度の発疹が認められている（4.8 項参照）。グレード 3 の発疹が認められた場合はイピリムマブとニボルマブの併用療法を

	中断し、グレード 4 の発疹が認められた場合は投与を中止する。重度の発疹は、メチルプレドニゾロン換算で 1～2 mg/kg/日の高用量コルチコステロイドで管理する。 SJS 及び TEN の稀な症例（一部は致死的転帰）が認められている。SJS 又は TEN の症状又は徴候が発現した場合は、イピリムマブとニボルマブの併用療法を中止し、評価及び治療のために専門医に相談する。イピリムマブとニボルマブの併用療法で SJS 又は TEN が発現した場合は、投与を永続的に中止することが推奨される（4.2 項参照）。 <u>免疫に関連した神経反応</u> *イピリムマブ単剤療法* イピリムマブは、重度の免疫に関連する神経学的な副作用を伴う。致死的なギラン・バレー症候群が臨床試験で報告されている。重症筋無力症様症状も報告されている（4.8 項参照）。患者は筋力低下を呈することがある。感覚ニューロパチーが発現することもある。 4 日間を超えて持続する原因不明の運動ニューロパチー、筋力低下又は感覚ニューロパチーを評価し、疾患進行、感染症、代謝症候群及び併用薬などの非炎症性の原因を除外する。イピリムマブとの因果関係が否定できない中等度（グレード 2）のニューロパチー（運動障害、感覚障害の有無を問わない）が認められた場合は、予定された投与を中断する。神経症状がベースラインまで回復した場合、イピリムマブの投与を再開してもよい（4.2 項参照）。 イピリムマブとの関連が疑われる重度（グレード 3 又は 4）の感覚ニューロパチーが認められた患者では、イピリムマブの投与を永続的に中止しなければならない（4.2 項参照）。感覚ニューロパチーの管理に関する実施医療機関のガイドラインに従って患者を治療し、コルチコステロイドの静脈内投与（例: メチルプレドニゾロン 2 mg/kg/日）を直ちに開始すること。 運動ニューロパチーの進行性の徴候は免疫に関連するものとみなし、それに応じて管理しなければならない。重度（グレード 3 又は 4）の運動ニューロパチーが認められた患者では、因果関係にかかわらずイピリムマブの投与を永続的に中止しなければならない（4.2 項参照）。 <u>免疫に関連した腎炎及び腎機能障害</u> *イピリムマブとニボルマブの併用* イピリムマブとニボルマブの併用療法において、重度の腎炎及び腎機能障害が認められている（4.8 項参照）。腎炎又は腎機能障害の徴候及び症状について患者をモニタリングすること。ほとんどの患者は、無症候性の血清クレアチニン増加を呈する。疾患に関連した原因を除外すること。 グレード 4 の血清クレアチニン増加が認められた場合は、イピリムマブとニボルマブの併用療法を永続的に中止し、メチルプレドニゾロン換算で 1～2 mg/kg/日の用量でコルチコステロイドの投与を開始する。

グレード 2 又は 3 の血清クレアチニン増加については、イピリムマブとニボルマブの併用療法を中断し、メチルプレドニゾロン換算で 0.5～1 mg/kg/日の用量でコルチコステロイドの投与を開始する。改善が認められた場合、コルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法を再開することができる。コルチコステロイドの投与開始にもかかわらず悪化又は改善が認められない場合は、コルチコステロイドをメチルプレドニゾロン換算で 1～2 mg/kg/日に増量し、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。

<u>免疫に関連した内分泌障害</u>

イピリムマブ単剤療法

イピリムマブは、下垂体炎、下垂体機能低下症、副腎機能不全、甲状腺機能低下症、1 型糖尿病及び糖尿病性ケトアシドーシスとして発現する内分泌系器官の炎症を引き起こす可能性があり（4.2 項及び 4.8 項参照）、患者は脳転移又は基礎疾患などの他の原因に類似した非特異的な症状を呈することがある。主な臨床症状は、頭痛及び疲労である。症状には、視野欠損、行動変化、電解質異常、低血圧なども含まれる。患者の症状の原因として、副腎クリーゼを除外しなければならない。イピリムマブに関連した内分泌障害の臨床経験は限られている。

MDX010-20 試験でイピリムマブ 3 mg/kg 単剤療法を受けた患者において、中等度から極めて重度（グレード 2～4）の免疫に関連した内分泌障害が発現するまでの期間は、投与開始から 7 週間から約 20 週間の範囲であった。臨床試験で認められた免疫に関連した内分泌障害は、免疫抑制療法及びホルモン補充療法により概ねコントロール可能であった。

重度の脱水、低血圧又はショックなどの副腎クリーゼの徴候が認められる場合は、鉱質コルチコイド活性を有するコルチコステロイドの静脈内投与を直ちに行うことが推奨され、敗血症又は感染の有無について患者を評価しなければならない。副腎機能不全の徴候があるが、副腎クリーゼには至っていない場合は、臨床検査及び画像評価を含む詳細な検査を検討する。コルチコステロイド療法の開始前に、内分泌機能を評価するための臨床検査結果の評価を実施してもよい。下垂体の画像検査又は内分泌機能の臨床検査で異常が認められた場合は、病変腺の炎症を治療するために高用量コルチコステロイドの短期投与（例: デキサメタゾン 4 mg を 6 時間ごと又は同等の薬剤）を行うことが推奨され、予定されたイピリムマブの投与を中断する（4.2 項参照）。副腎機能障害がコルチコステロイド療法によって回復するかどうかは現時点では不明である。適切なホルモン補充療法も開始すること。長期のホルモン補充療法が必要となる場合がある。

症候性糖尿病の場合、イピリムマブの投与を中断し、必要に応じてインスリン補充療法を開始する。適切なインスリン補充療法を確実に実施するために、血糖値のモニタリングを継続すること。生命を脅かす糖尿病が発現した場合は、イピリムマブの投与を永続的に中止しなければならない。

症状又は臨床検査値異常がコントロールされ、患者の全般症状の改善が確認されれば、イピリムマブの投与を再開することができ、臨床的判断に基づいてコルチコステロイドの漸減を開始する。漸減は 1 ヵ月以上かけて行う。

	イピリムマブとニボルマブの併用 イピリムマブとニボルマブの併用療法により、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）、糖尿病及び糖尿病性ケトアシドーシスを含む重度の内分泌障害が認められている（4.8 項参照）。 内分泌障害の臨床徴候及び症状、高血糖及び甲状腺機能の変化について、患者をモニタリングすること（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）。患者は、疲労、頭痛、精神状態変化、腹痛、異常な排便習慣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類似した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みなす。 症候性の甲状腺機能低下症が認められた場合、イピリムマブとニボルマブの併用療法は中断し、必要に応じて甲状腺ホルモンの補充療法を開始する。症候性の甲状腺機能亢進症が認められた場合、イピリムマブとニボルマブの併用療法は中断し、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は、メチルプレドニゾロン換算で 1～2 mg/kg/日のコルチコステロイドを投与することも検討する。改善が認められた場合、必要に応じてコルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法を再開することができる。ホルモン補充療法が適切に行われていることを確認するために、甲状腺機能のモニタリングを継続すること。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発現した場合は、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。 グレード 2 の症候性の副腎機能不全が認められた場合、イピリムマブとニボルマブの併用療法は中断し、必要に応じて生理的コルチコステロイドの補充療法を開始する。重度（グレード 3）又は生命を脅かす（グレード 4）副腎機能不全が発現した場合は、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。副腎機能及びホルモン濃度のモニタリングを継続し、コルチコステロイドの補充療法が適切に行われていることを確認する。 グレード 2 又は 3 の症候性の下垂体炎の場合、イピリムマブとニボルマブの併用療法は中断し、必要に応じてホルモン補充療法を開始する。下垂体の急性炎症が疑われる場合は、メチルプレドニゾロン換算で 1～2 mg/kg/日のコルチコステロイドの投与も検討する。改善が認められた場合、必要に応じてコルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法を再開することができる。生命を脅かす（グレード 4）下垂体炎が発現した場合は、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。下垂体機能及びホルモン濃度を継続的にモニタリングし、ホルモン補充療法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、イピリムマブとニボルマブの併用療法は中断し、必要に応じてインスリン補充療法を開始する。適切なインスリン補充療法を確実に行うために、血糖値のモニタリングを継続すること。生命を脅かす糖尿病が発現した場合は、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。

	Infusion reaction *イピリムマブ単剤療法又はニボルマブとの併用療法* イピリムマブ又はイピリムマブとニボルマブの併用療法の臨床試験において、重度の Infusion reaction が報告されている（4.8 項参照）。重度又は生命を脅かす Infusion reaction が発現した場合は、イピリムマブの投与又はイピリムマブとニボルマブの点滴静注の併用を中止し、適切な薬物療法を実施しなければならない。軽度又は中等度の Infusion reaction が発現した患者には、イピリムマブの投与又はイピリムマブとニボルマブの併用療法を行うことができるが、その際は、Infusion reaction の予防のため、各国の治療ガイドラインに従って、綿密なモニタリング及び前投薬を行うこと。 その他の免疫に関連した副作用 *イピリムマブ単剤療法* MDX010-20 試験において、イピリムマブ 3 mg/kg 単剤療法を受けた患者で免疫との関連性が疑われる次の副作用が報告されている: ぶどう膜炎、好酸球増加症、リパーゼ増加及び糸球体腎炎。また、MDX010-20 試験において、イピリムマブ 3 mg/kg 及び gp100 ペプチドワクチンを投与した患者において、虹彩炎、溶血性貧血、アミラーゼ増加、多臓器不全及び肺臓炎が報告されている。市販後にフォークト・小柳・原田病、漿液性網膜剥離及び非感染性膀胱炎の症例が報告されている（4.2 項及び 4.8 項参照）。 これらの反応が重度（グレード 3 又は 4）の場合は、直ちに高用量コルチコステロイドの全身投与及びイピリムマブの投与中止が必要となることがある（4.2 項参照）。イピリムマブに関連するぶどう膜炎、虹彩炎、漿液性網膜剥離又は上強膜炎については、医学的に必要であれば、コルチコステロイド点眼薬の使用を検討する。イピリムマブに関連する眼の炎症を有する患者で、一過性の視力低下が報告されている。 イピリムマブの投与を受けた患者において、固形臓器移植拒絶反応が市販後に報告されている。イピリムマブの投与により、固形臓器移植患者における拒絶反応のリスクが増加する可能性がある。これらの患者では、イピリムマブ投与のベネフィットと臓器拒絶反応のリスクを比較検討すること。 *イピリムマブの単剤療法又は PD-1 又は PD-L1 阻害剤との併用療法* 血球貪食性リンパ組織球症（HLH）が、イピリムマブの単剤療法及びイピリムマブと PD-1 又は PD-L1 阻害剤との併用療法（ニボルマブとの併用療法を含む）で認められている。イピリムマブを単剤療法、あるいは PD-1 又は PD-L1 阻害剤と併用して投与する場合は注意が必要である。HLH が確認された場合、イピリムマブの投与又はイピリムマブと PD-1 又は PD-L1 阻害剤との併用療法を中止し、HLH に対する治療を開始する。 *イピリムマブとニボルマブの併用* イピリムマブとニボルマブを併用した臨床試験において、用量及び腫瘍の種類を問わず、1%未満の患者で次の免疫に関連した副作用が報告された: 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。市販後にフォークト・小柳・原田病、漿液性網膜剥離及び非感染性膀胱炎の症例が報告されている（4.2 項及び 4.8 項参照）。イピリムマブに関連する眼の炎症を有する患者で一過性の視力低下が報告されている。

免疫に関連した副作用が疑われる場合は、病因を確認するか、他の原因を除外するために適切な評価を行う。副作用の重症度に基づき、イピリムマブとニボルマブの併用療法を中断し、コルチコステロイドを投与する。改善が認められた場合、コルチコステロイドの漸減後にイピリムマブとニボルマブの併用療法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は、イピリムマブとニボルマブの併用療法を永続的に中止しなければならない。

イピリムマブとニボルマブの併用療法では、致死的転帰を伴う筋毒性（筋炎、心筋炎、横紋筋融解症）の症例が報告されている。患者が筋毒性の徴候及び症状を発現した場合は、綿密なモニタリングを実施し、速やかに専門医に相談して評価及び治療を受けさせること。筋毒性の重症度に基づき、イピリムマブとニボルマブの併用療法は中断又は中止し（4.2 項参照）、適切な治療を開始する。

心筋炎の診断には高度の疑い指標が必要である。心臓又は心肺の症状が認められる患者では、心筋炎の可能性について評価すること。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て心臓専門医の診察及び診断検査を速やかに実施する。心筋炎の診断が確定した場合、イピリムマブとニボルマブの併用療法は中断又は永続的に中止すること（4.2 項参照）。

<u>疾患に特異的な注意</u>

悪性黒色腫

眼部の悪性黒色腫、原発性 CNS 悪性黒色腫、及び活動性脳転移を有する患者は MDX010-20 試験に組み入れられなかった（5.1 項参照）。

眼部の悪性黒色腫患者は、CA184-169 試験に組み入れなかった。ただし、脳転移を有する患者のうち、転移性脳病変に関連する神経症状が認められず、イピリムマブの投与開始前 10 日間に全身性コルチコステロイド療法を必要としない、又は受けていない患者は、本試験に組み入れられた（5.1 項参照）。

眼部の悪性黒色腫、活動性脳転移、及びイピリムマブによる治療歴を有する患者は、小児を対象とした CA184-070 試験には組み入れなかった（5.1 項参照）。

小児を対象とした CA184-178 試験では、眼部の悪性黒色腫、活動性脳転移、及び CTLA4、PD-1、PD-L1 又は CD137 を標的とした薬剤による前治療歴を有する患者は組み入れなかった（5.1 項参照）。

ベースライン時のパフォーマンススコアが 2 以上の患者、活動性の脳転移又は自己免疫疾患を有する患者、及び試験登録前に全身性免疫抑制剤の投与を受けていた患者

	は、イピリムマブとニボルマブの併用療法の臨床試験から除外した。眼部/ブドウ膜の悪性黒色腫患者は、悪性黒色腫の臨床試験から除外された。データがないため、これらの集団に対するニボルマブの使用は、個々の患者で潜在的なベネフィット/リスクを注意深く検討した上で慎重に行う必要がある。 ニボルマブ単剤療法と比較して、イピリムマブとニボルマブの併用療法による PFS の延長は、PD-L1 発現率が低い患者においてのみ確立されている。PD-L1 発現率の高い（PD-L1 ≥ 1%）患者においては、イピリムマブとニボルマブの併用療法とニボルマブ単剤療法の OS の改善は同程度であった。併用療法を開始する前に、ニボルマブ単剤療法と比較して、併用療法のベネフィット及び毒性を考慮し、各患者及び腫瘍の特性を注意深く評価することが推奨される（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おけるイピリムマブとニボルマブの併用療法* 急速な病勢進行を呈する疾患を有する患者では、治療を開始する前にイピリムマブとニボルマブの併用による効果発現の遅発性を考慮すること（5.1 項参照）。 *腎細胞癌* イピリムマブとニボルマブを併用する臨床試験では、脳転移の合併、活動性の自己免疫疾患又は全身免疫抑制を必要とする疾患の既往を有する患者は除外した（4.5 項及び 5.1 項参照）。データがないため、これらの集団におけるイピリムマブとニボルマブの併用療法は、各患者で潜在的なベネフィット/リスクを注意深く検討した上で慎重に実施する必要がある。 *非小細胞肺癌* 活動性の自己免疫疾患、症候性の間質性肺疾患、全身性の免疫抑制を必要とする疾患、活動性（未治療）の脳転移を有する患者、進行性疾患に対する全身治療歴を有する患者、感作性 EGFR 変異又は ALK 転座を有する患者は、NSCLC の一次治療を対象としたピボタル試験から除外した（4.5 項及び 5.1 項参照）。高齢患者（75 歳以上）に関するデータは限られている（5.1 項参照）。これらの患者では、イピリムマブとニボルマブ及び化学療法の併用療法は、各患者で潜在的なベネフィット・リスクを注意深く検討した上で慎重に使用する必要がある。 *悪性胸膜中皮腫* 未分化腹膜中皮腫、心膜中皮腫、精巣中皮腫、精巣鞘膜中皮腫、間質性肺疾患、活動性自己免疫疾患、全身免疫抑制を必要とする疾患、及び脳転移を有する患者は、MPM の一次治療を対象としたピボタル試験から除外した（4.5 項及び 5.1 項参照）。データがないため、これらの集団におけるイピリムマブとニボルマブの併用療法は、各患者で潜在的なベネフィット/リスクを注意深く検討した上で慎重に実施する必要がある。 *dMMR 又は MSI-H を有する結腸・直腸癌* ベースライン時のパフォーマンススコアが 2 以上の患者、活動性の脳転移又は軟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必要とする疾患を有する患者は、dMMR 又は MSI-H を有する転移性 CRC を対象とした臨床試験から除外した（4.5 項及び 5.1 項参照）。データがないため、これらの集団における

	イピリムマブとニボルマブの併用療法は、各患者で潜在的なベネフィット/リスクを注意深く検討した上で慎重に実施する必要がある。 *食道扁平上皮癌* ベースライン時のパフォーマンススコアが 2 以上の患者、脳転移の合併、活動性自己免疫疾患の既往、全身免疫抑制を必要とする疾患、又は食道腫瘍に隣接する臓器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 を対象とした臨床試験から除外した（4.5 項及び 5.1 項参照）。データがないため、これらの集団におけるイピリムマブとニボルマブの併用療法は、各患者で潜在的なベネフィット/リスクを注意深く検討した上で慎重に実施する必要がある。 一次治療の OSCC 試験では、イピリムマブとニボルマブの併用療法は、化学療法と比較して 4 ヵ月以内の死亡数が多かった。予後不良及び/又は進行性疾患の患者においては、治療を開始する前に、イピリムマブとニボルマブの併用療法の効果発現の遅発性を考慮すべきである（5.1 項参照）。 *肝細胞癌* ベースライン時の ECOG パフォーマンススコアが 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、肝性脳症歴（無作為化後 12 ヵ月以内）、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、全身性の免疫抑制を必要とする疾患を有する患者は、HCC を対象とした臨床試験から除外された（4.5 項及び 5.1 項参照）。Child-Pugh 分類 B の HCC 患者において利用可能なデータは限られている。データがないため、これらの患者集団に対してイピリムマブとニボルマブの併用療法後にニボルマブを投与する場合は、個々の患者で潜在的なベネフィット／リスクを注意深く検討した上で、慎重に行う必要がある。 HCC では、イピリムマブとニボルマブの併用療法において、レンバチニブ又はソラフェニブと比較して 6 ヵ月以内の死亡数が多かった。死亡リスクの高さは予後不良因子と関連している可能性がある。予後不良因子を有する患者に対してイピリムマブとニボルマブの併用療法を開始する前に、医師はこのリスクを考慮すべきである。 <u>自己免疫疾患を有する患者</u> 自己免疫疾患の既往歴を有する患者（白斑及び甲状腺機能低下症などの内分泌障害が適切にコントロールされている患者を除く）は、既存の活動性自己免疫疾患又は臓器移植の移植片維持のために全身免疫抑制療法を必要とする患者を含め、臨床試験で評価されていない。イピリムマブは免疫応答を促進する T 細胞増強薬であり（5.1 項参照）、免疫抑制療法を阻害し、基礎疾患の悪化や移植片拒絶反応のリスクを高める可能性がある。重度の活動性自己免疫疾患を有し、さらなる免疫活性化が生命を脅かすおそれのある患者においては、イピリムマブの投与は避けること。その他の自己免疫疾患の既往歴を有する患者では、各患者で潜在的なリスク・ベネフィットを注意深く検討した上でイピリムマブを慎重に投与すること。

	ナトリウム制限食の患者 本剤は、10 mL バイアルあたりナトリウム 23 mg、40 mL バイアルあたりナトリウム 92 mg を含有する。これは、WHO が推奨する成人のナトリウムの最大 1 日摂取量 2 g のそれぞれ 1.15%及び 4.60%に相当する。ナトリウム制限食を受けている患者を治療する際には考慮すること。 ベムラフェニブとの同時投与 第 1 相試験において、イピリムマブ（3 mg/kg）とベムラフェニブ（960 mg BID 又は 720 mg BID）の同時投与により、無症候性のグレード 3 のトランスアミナーゼ増加（ALT/AST が ULN の 5 倍超）及びビリルビン増加（総ビリルビンが ULN の 3 倍超）が報告された。これらの予備的データに基づき、イピリムマブとベムラフェニブの同時投与は推奨されない。 ベムラフェニブとの逐次投与 第 2 相試験において、BRAF 遺伝子変異を有する転移性悪性黒色腫患者を対象に、ベムラフェニブ投与後にイピリムマブ 10 mg/kg を逐次投与したところ、イピリムマブ単剤投与と比較してグレード 3 以上の皮膚の副作用の発現率が高かった。ベムラフェニブによる前治療後にイピリムマブを投与する場合は注意すること。
副作用	*イピリムマブ単剤療法（4.2 項参照）* a. 安全性プロファイルの要約 イピリムマブは、様々な用量及び腫瘍の種類での使用を評価する臨床プログラムにおいて、約 10,000 例の患者にイピリムマブが投与されている。特に明記しない限り、以下のデータは悪性黒色腫の臨床試験におけるイピリムマブ 3 mg/kg の曝露量を反映している。第 3 相試験 MDX010-20（5.1 項参照）では、患者の投与回数の中央値は 4 回（範囲: 1～4）であった。 イピリムマブは、免疫活性の亢進又は過剰な免疫活性に起因する副作用を伴うことが最も多い。重篤な副作用を含むこれらの副作用のほとんどは、適切な薬物療法の開始又はイピリムマブの投与中止後に回復した（免疫に関連した副作用の管理については 4.4 項を参照）。 MDX010-20 試験でイピリムマブ 3 mg/kg 単剤療法を受けた患者において、最も頻繁に報告された副作用（10%以上）は、下痢、発疹、そう痒症、疲労、悪心、嘔吐、食欲減退及び腹痛であった。大部分は軽度から中等度（グレード 1 又は 2）であった。10%の患者が副作用により*イピリムマブ*の投与を中止した。 b. 副作用一覧表 臨床試験（n=767）及び市販後調査でイピリムマブ 3 mg/kg を投与された進行性悪性黒色腫患者において報告された副作用を表 6 に示す。

これらの反応を器官別大分類及び発現頻度ごとに示す。発現頻度は以下のとおり定義する。極めて高頻度（1/10 以上）、高頻度（1/100 以上 1/10 未満）、低頻度（1/1,000 以上 1/100 未満）、稀（1/10,000 以上 1/1,000 未満）、極めて稀（1/10,000 未満）、不明（利用可能な市販後データからの推定不能）。各発現頻度カテゴリー内の副作用は、重症度の高い順に示す。MDX010-20 試験でイピリムマブの投与を受けた HLA-A2*0201 陽性患者における免疫に関連した副作用の発現率は、臨床試験全体で認められた発現率と同程度であった。

第 2 相及び第 3 相臨床試験で集積された化学療法による治療歴のない患者（投与例 N=75）、2 つの後ろ向き観察研究における治療歴のない患者（N=273 及び N=157）、並びに CA184-169 試験における患者（N=362）において、イピリムマブ 3 mg/kg の安全性プロファイルは、前治療歴のある進行性悪性黒色腫患者と同様であった。

国際共同前向き観察研究 CA184-143（N=1151）に登録された切除不能又は転移性悪性黒色腫患者にイピリムマブを投与（3 mg/kg、3 年間以上の追跡調査）したときの安全性データは、進行性悪性黒色腫を対象としたイピリムマブの臨床試験で報告されているものと同様であった。

表 6: イピリムマブ 3 mg/kg を投与した進行性悪性黒色腫患者における副作用 [a]

感染症及び寄生虫症	
高頻度	敗血症 [b]、尿路感染症、気道感染症
低頻度	敗血症性ショック [b]、肺炎
良性、悪性及び詳細不明の新生物（嚢胞及びポリープを含む）	
高頻度	腫瘍疼痛
低頻度	腫瘍随伴症候群
血液及びリンパ系障害	
高頻度	貧血、リンパ球減少症、血小板減少症、好中球減少症
低頻度	溶血性貧血 [b]、好酸球増加症
不明	血球貪食性リンパ組織球症 [e]
免疫系障害	
低頻度	過敏症
極めて稀	アナフィラキシー反応
不明	固形臓器移植拒絶反応 [e]
内分泌障害	
高頻度	下垂体機能低下症（下垂体炎を含む）[c]、甲状腺機能低下症 [c]
低頻度	副腎機能不全 [c]、続発性副腎皮質機能不全 [d]、甲状腺機能亢進症 [c]、性腺機能低下症
稀	自己免疫性甲状腺炎 [d]、甲状腺炎 [d]
代謝及び栄養障害	
極めて高頻度	食欲減退

	高頻度	脱水、低カリウム血症、体重減少、低ナトリウム血症
	低頻度	アルカローシス、低リン酸血症、腫瘍崩壊症候群、低カルシウム血症[d]
	稀	1 型糖尿病（糖尿病性ケトアシドーシスを含む）[h]
	精神障害	
	高頻度	錯乱状態、うつ病
	低頻度	精神状態の変化、性欲減退
	神経系障害	
	高頻度	末梢性感覚ニューロパチー、浮動性めまい、頭痛、嗜眠、脳ニューロパチー、脳浮腫、末梢性ニューロパチー
	低頻度	ギラン・バレー症候群[b, c]、髄膜炎（無菌性）、自己免疫性中枢性ニューロパチー（脳炎）[d]、失神、運動失調、振戦、ミオクローヌス、構語障害
	稀	重症筋無力症[d]
	不明	脊髄炎
	眼障害	
	高頻度	霧視、眼痛
	低頻度	ぶどう膜炎[c]、硝子体出血、虹彩炎[c]、眼の浮腫[d]、眼瞼炎[d]、視力低下、眼の異物感、結膜炎
	稀	フォークト・小柳・原田病[e]、漿液性網膜剥離
	心臓障害	
	高頻度	不整脈、心房細動
	血管障害	
	高頻度	低血圧、潮紅、ほてり
	低頻度	血管炎、血管障害[b]、末梢性虚血、起立性低血圧
	稀	側頭動脈炎[d]
	呼吸器、胸郭及び縦隔障害	
	高頻度	呼吸困難、咳嗽、アレルギー性鼻炎
	低頻度	呼吸不全、急性呼吸窮迫症候群[b]、肺浸潤、肺水腫、肺臓炎
	胃腸障害	
	極めて高頻度	下痢[c]、嘔吐、悪心、便秘、腹痛
	高頻度	胃腸出血、大腸炎[b, c]、胃食道逆流性疾患、粘膜の炎症[d]、胃腸炎、口内炎
	低頻度	消化管穿孔[b, c]、大腸穿孔[b, c]、腸管穿孔[b, c]、腹膜炎[b]、憩室炎、膵炎、腸炎、胃潰瘍、大腸潰瘍、食道炎、イレウス[d]、直腸炎[d]
	稀	膵外分泌機能不全、セリアック病
	肝胆道系障害	
	高頻度	肝機能異常
	低頻度	肝不全[b, c]、肝炎、肝腫大、黄疸

皮膚及び皮下組織障害	
極めて高頻度	発疹[c]、そう痒症[c]
高頻度	皮膚炎、紅斑、尋常性白斑、蕁麻疹、湿疹[d]、脱毛症、寝汗、皮膚乾燥
低頻度	中毒性表皮壊死融解症[b,c]、白血球破砕性血管炎、皮膚剥脱、毛髪変色変化[d]
稀	多形紅斑[d]、乾癬[d]、好酸球増加と全身症状を伴う薬物反応（DRESS）[d]
不明	類天疱瘡
筋骨格系及び結合組織障害	
極めて高頻度	筋骨格系疼痛[f]
高頻度	関節痛、筋肉痛、筋痙縮、関節炎
低頻度	リウマチ性多発筋痛、筋炎[d]、筋力低下[d]
稀	多発性筋炎[d]
腎及び尿路障害	
高頻度	腎不全[b]
低頻度	糸球体腎炎[c]、自己免疫性腎炎[d]、尿細管性アシドーシス、血尿[d]、非感染性膀胱炎[g]、蛋白尿[d]
生殖系及び乳房障害	
低頻度	無月経
一般・全身障害及び投与部位の状態	
極めて高頻度	疲労、注射部位反応、発熱、浮腫、疼痛
高頻度	悪寒、無力症、インフルエンザ様疾患[d]
低頻度	多臓器不全[b,c]、全身性炎症反応症候群[d]、注入に伴う反応
臨床検査	
高頻度	アラニンアミノトランスフェラーゼ増加[c]、アスパラギン酸アミノトランスフェラーゼ増加[c]、血中アルカリホスファターゼ増加[d]、血中ビリルビン増加、リパーゼ増加[c]
低頻度	γ-グルタミルトランスフェラーゼ増加[d]、血中クレアチニン増加、血中甲状腺刺激ホルモン増加、血中コルチゾール減少、血中コルチコトロピン減少、血中アミラーゼ増加[c]、抗核抗体陽性[d]、血中テストステロン減少
稀	血中甲状腺刺激ホルモン減少[d]、サイロキシン減少[d]、血中プロラクチン異常[d]

表 6 に示した副作用の発現頻度は、イピリムマブに必ず起因するものではなく、基礎疾患の影響が含まれている可能性がある。

[a] 発現頻度は、悪性黒色腫を対象にイピリムマブ 3 mg/kg を検討した 9 つの臨床試験の集積データに基づく。

[b] 致死的転帰を含む。

[c] これらの潜在的な炎症性の副作用に関する追加情報を「特定の副作用の説明」及び 4.4 項に示す。これらの項に示すデータは主に第 3 相試験（MDX010-20）のデータを反映している。
[d] 発現頻度の算出には、悪性黒色腫を対象とした 9 つの完了した臨床試験以外のデータも含まれている。
[e] 市販後の事象（4.4 項も参照のこと）。
[f] 筋骨格痛は、背部痛、骨痛、筋骨格系胸痛、筋骨格不快感、筋肉痛、頚部痛、四肢痛及び脊椎痛を含む複合用語である。
[g] 臨床試験及び市販後の使用で報告されている。
[h] 糖尿病性ケトアシドーシスを伴う可能性のある 1 型糖尿病

表 6 に記載されていないその他の副作用は、悪性黒色腫の臨床試験において他の用量（3 mg/kg 未満又は 3 mg/kg 超）のイピリムマブを投与された患者で報告されている。これらのその他の副作用の発現頻度は、特記しない限り 1%未満であった。髄膜症、心筋炎、心嚢液貯留、心筋症、自己免疫性肝炎、結節性紅斑、自己免疫性膵炎、下垂体機能亢進症、副甲状腺機能低下症、感染性腹膜炎、上強膜炎、強膜炎、レイノー現象、手掌・足底発赤知覚不全症候群、サイトカイン放出症候群、サルコイドーシス、血中ゴナドトロピン減少、白血球減少症、赤血球増加症、リンパ球増加症、眼筋炎及び感音性聴力低下。

臨床試験 CA184-169（N=362）におけるイピリムマブ 3 mg/kg の全般的な安全性プロファイルは、進行性悪性黒色腫の治療を受けた患者においてイピリムマブで確立されたものと一致していた。

イピリムマブとニボルマブ併用療法（化学療法併用又は非併用）（4.2 項参照）

a. 安全性プロファイルの要約

イピリムマブを併用投与する場合、投与開始前に他の治療薬の SmPC を参照すること。イピリムマブと併用する他の治療薬の安全性プロファイルに関する詳細情報については、各 SmPC を参照のこと。

最短追跡調査期間が 6～47 ヵ月の様々な腫瘍の種類を有する患者（n=2626）でイピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を実施した集積データセットにおいて、最も高頻度（10%以上）に認められた副作用は、疲労（47%）、下痢（35%）、発疹（37%）、悪心（27%）、そう痒症（29%）、筋骨格痛（26%）、発熱（23%）、食欲減退（22%）、咳嗽（21%）、腹痛（18%）、嘔吐（18%）、便秘（18%）、関節痛（18%）、呼吸困難（17%）、甲状腺機能低下症（16%）、頭痛（15%）、上気道感染（13%）、浮腫（13%）及び浮動性めまい（10%）であった。イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）におけるグレード 3～5 の副作用の発現率は 66%であり、治験薬との因果関係が否定できない致死的な副作用は 1.0%であった。悪性黒色腫に対してイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併用投与した患者において、イピリムマブとニボルマブを併用投与した集積データセット（化学療法の併用又は非併用）で報告された発現率よりも 10%以上高い発現率で報告された事象は、疲労（62%）、発疹（57%）、下痢（52%）、悪心（42%）、そう痒症（40%）、発熱（36%）及び頭痛（26%）であった。NSCLC に対してイピリムマブ 1 mg/kg とニボルマブ 360 mg 及び化学療法を併用投与した患者に

おいて、イピリムマブとニボルマブを併用投与した集積データセット（化学療法の併用又は非併用）で報告された発現率よりも 10%以上高い発現率で報告された事象は、貧血（32%）及び好中球減少症（15%）であった。

b. 副作用の概要表

イピリムマブとニボルマブ併用療法（化学療法の併用又は非併用）の集積データセット（n=2626）及び市販後に報告された副作用を表 7 に示す。これらの反応を器官別大分類別及び発現頻度ごとに示す。発現頻度は以下のとおり定義する。極めて高頻度（1/10 以上）、高頻度（1/100 以上 1/10 未満）、低頻度（1/1,000 以上 1/100 未満）、稀（1/10,000 以上 1/1,000 未満）、極めて稀（1/10,000 未満）、不明（利用可能な市販後データからの推定不能）。各発現頻度カテゴリー内の副作用は、重症度の高い順に示す。

表 7: イピリムマブと他の治療薬との併用による副作用

	ニボルマブとの併用（化学療法の併用又は非併用）
感染症及び寄生虫症	
極めて高頻度	上気道感染
高頻度	肺炎、気管支炎、結膜炎
稀	無菌性髄膜炎
血液及びリンパ系障害	
極めて高頻度	貧血[b,i]、血小板減少症[b]、白血球減少症[b]、リンパ球減少症[b]、好中球減少症[b]
高頻度	好酸球増加症
低頻度	発熱性好中球減少症
不明	血球貪食性リンパ組織球症
免疫系障害	
高頻度	注入に伴う反応（サイトカイン放出症候群を含む）、過敏症
稀	サルコイドーシス
不明	固形臓器移植拒絶反応[f]
内分泌障害	
極めて高頻度	甲状腺機能低下症
高頻度	甲状腺機能亢進症、甲状腺炎、副腎機能不全、下垂体炎、下垂体機能低下症、糖尿病
低頻度	糖尿病性ケトアシドーシス
稀	副甲状腺機能低下症
代謝及び栄養障害	
極めて高頻度	食欲減退、高血糖[b]、低血糖[b]
高頻度	脱水、低アルブミン血症、低リン酸血症、体重減少
低頻度	代謝性アシドーシス

不明	腫瘍崩壊症候群 [g]
神経系障害	
極めて高頻度	頭痛
高頻度	浮動性めまい、末梢性ニューロパチー
低頻度	多発ニューロパチー、腓骨神経麻痺、自己免疫性ニューロパチー（顔面及び外転神経不全麻痺を含む）、脳炎、重症筋無力症
稀	ギラン・バレー症候群、神経炎、脊髄炎（横断性脊髄炎を含む）
眼障害	
高頻度	霧視、眼乾燥
低頻度	ぶどう膜炎、上強膜炎
稀	フォークト・小柳・原田病、漿液性網膜剥離
心臓障害	
高頻度	頻脈、心房細動
低頻度	心筋炎 [a]、不整脈（心室性不整脈を含む）[a]、徐脈
不明	心膜の障害 [h]
血管障害	
高頻度	高血圧
呼吸器、胸郭及び縦隔障害	
極めて高頻度	咳嗽、呼吸困難
高頻度	肺臓炎 [a]、肺塞栓 [a]、胸水
胃腸障害	
極めて高頻度	下痢、嘔吐、悪心、腹痛、便秘
高頻度	大腸炎 [a]、膵炎、口内炎、胃炎、口内乾燥
低頻度	十二指腸炎
稀	腸管穿孔 [a]、膵外分泌機能不全、セリアック病
肝胆道系障害	
高頻度	肝炎
皮膚及び皮下組織障害	
極めて高頻度	発疹 [c]、そう痒症
高頻度	脱毛症、尋常性白斑、蕁麻疹、皮膚乾燥、紅斑
低頻度	スティーヴンス・ジョンソン症候群、多形紅斑、乾癬、その他の苔癬型疾患 [j]
稀	中毒性表皮壊死融解症 [a, d]、硬化性苔癬
筋骨格系及び結合組織障害	
極めて高頻度	筋骨格系疼痛 [e]、関節痛
高頻度	筋痙縮、筋力低下、関節炎
低頻度	リウマチ性多発筋痛症、ミオパチー、筋炎（多発性筋炎を含む）[a]
稀	脊椎関節症、シェーグレン症候群、横紋筋融解症 [a]

腎及び尿路障害	
高頻度	腎不全（急性腎障害を含む）[a]
低頻度	尿細管間質性腎炎、腎炎
稀	非感染性膀胱炎
一般・全身障害及び投与部位の状態	
極めて高頻度	疲労、発熱、浮腫（末梢性浮腫を含む）
高頻度	胸痛、疼痛、悪寒
臨床検査	
極めて高頻度	アルカリホスファターゼ増加[b]、AST 増加[b]、ALT 増加[b]、総ビリルビン増加[b]、クレアチニン増加[b]、アミラーゼ増加[b]、リパーゼ増加[b]、低ナトリウム血症[b]、高カリウム血症[b]、低カリウム血症[b]、高カルシウム血症[b]、低カルシウム血症[b]
高頻度	高ナトリウム血症[b]、高マグネシウム血症[b]、甲状腺刺激ホルモン増加、γ-グルタミルトランスフェラーゼ増加

表 7 に示した副作用の発現頻度は、イピリムマブの単剤療法又は他の治療薬との併用療法に必ず起因するものではなく、基礎疾患又は併用される医薬品に起因する可能性がある。

[a] 完了又は実施中の臨床試験において、死亡例が報告されている。
[b] 臨床検査値に関する事象の発現頻度は、臨床検査値がベースラインから悪化した患者の割合を示す。下記の「特定の副作用に関する叙述；臨床検査値異常」を参照すること。
[c] 発疹は、斑状丘疹状皮疹、紅斑性皮疹、そう痒性皮疹、毛孔性皮疹、斑状皮疹、麻疹様皮疹、丘疹性皮疹、膿疱性皮疹、丘疹鱗屑性皮疹、小水疱性皮疹、全身性皮疹、剥脱性皮疹、皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、アトピー性皮膚炎、水疱性皮膚炎、剥脱性皮膚炎、乾癬様皮膚炎、薬疹、結節性皮疹及び類天疱瘡を含む複合用語である。
[d] 集積データセットの対象外の試験でも報告されている。発現頻度は臨床プログラム全体の曝露に基づく。
[e] 筋骨格痛は、背部痛、骨痛、筋骨格系胸痛、筋骨格不快感、筋肉痛、肋間筋痛、頚部痛、四肢痛及び脊椎痛を含む複合用語である。
[f] 市販後の事象（4.4 項も参照のこと）。
[g] 臨床試験及び市販後の使用で報告されている。
[h] 心膜障害は、心膜炎、心嚢液貯留、心タンポナーデ、ドレスラー症候群を含む複合用語である。
[i] 貧血は、溶血性貧血及び自己免疫性貧血、ヘモグロビン減少、鉄欠乏性貧血、赤血球数減少を含む複合用語である。
[j] 苔癬疾患は、角化性苔癬と扁平苔癬を含む複合用語である。

<u>特定の副作用に関する叙述</u>

特記しない限り、イピリムマブの単剤療法に関連するデータは、進行性（切除不能又は転移性）悪性黒色腫を対象とした第 3 相試験（MDX010-20、第 5.1 項を参照）において、イピリムマブ 3 mg/kg の単剤療法（n=131）又はイピリムマブ 3 mg/kg と gp100 の併用療法（n=380）を受けた患者に基づく。

イピリムマブとの併用療法は、免疫に関連した副作用を伴う。免疫に関連した副作用は、ほとんどの場合、適切な薬物療法により回復した。イピリムマブとニボルマブの併用療法を受けた患者では、ニボルマブの単剤療法を受けた患者と比較して、一般に永続的な投与の中止が必要となる割合が高かった。免疫に関連した副作用が発現し、投与を中止した患者の割合を表 8 に示す。また、有害事象を発現した患者について、高用量コルチコステロイド（プレドニゾン換算で 40 mg/日以上）を必要とした患者の割合を表 8 に示す。これらの副作用の管理ガイドラインは 4.4 項に記載する。

表 8: 投与中止又は高用量コルチコステロイドを必要とした免疫に関連した副作用

	イピリムマブとニボルマブの併用（化学療法の併用又は非併用） %
投与中止に至った、免疫に関連した副作用	
肺臓炎	2.1
大腸炎	6
肝炎	5
腎炎及び腎機能障害	1.1
内分泌障害	2.2
皮膚	1.0
過敏症/Infusion reaction	0.3
高用量コルチコステロイドを必要とした、免疫に関連した副作用 [a, b]	
肺臓炎	59
大腸炎	32
肝炎	39
腎炎及び腎機能障害	27
内分泌障害	18
皮膚	8
過敏症/Infusion reaction	18

[a] プレドニゾン換算で 40 mg/日以上
[b] 発現頻度は、免疫に関連した副作用を発現した患者数に基づく

免疫に関連した消化管反応

イピリムマブは、免疫に関連した重度の消化管反応を伴う。イピリムマブ 3 mg/kg と gp100 を併用投与した患者の 1%未満において、消化管穿孔による死亡が報告されている。

イピリムマブ 3 mg/kg 単剤療法群では、重症度を問わない下痢及び大腸炎がそれぞれ 27%及び 8%として報告された。重度（グレード 3 又は 4）の下痢及び重度（グレード 3 又は 4）の大腸炎の発現頻度はそれぞれ 5%であった。重度又は致死的（グレード 3～5）の免疫に関連した消化管反応が発現するまでの期間の中央値は、投与開始から 8 週間（範囲: 5～13 週間）であった。治験実施計画書に規定された管理ガイドラインにより、ほとんどの症例（90%）において回復（軽度［グレード 1］以下又はベースラ

	イン時の重症度まで改善と定義）が認められ、発現から回復までの期間の中央値は 4 週間（範囲: 0.6～22 週間）であった。臨床試験では、免疫に関連した大腸炎は粘膜の炎症（潰瘍の有無を問わない）並びにリンパ球及び好中球の浸潤を伴っていた。 *免疫に関連した大腸炎* イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者において、下痢又は大腸炎の発現率は 26.0%（682/2626 例）であった。グレード 2、3 及び 4 の有害事象は、それぞれ 8.1%（212/2626 例）、6.4%（167/2626 例）及び 0.2%（4/2626 例）として報告された。2 例（0.1%未満）が死亡した。発現までの期間の中央値は 1.4 ヵ月（範囲: 0.0～48.9 ヵ月）であった。618 例（91%）で回復が認められ、回復までの期間の中央値は 2.9 週間（範囲: 0.1～170.0+週間）であった。悪性黒色腫に対してイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併用投与した患者では、下痢又は大腸炎の発現率は 46.7%であり、グレード 2（13.6%）、グレード 3（15.8%）及びグレード 4（0.4%）が含まれる。 *免疫に関連した肺臓炎* イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者において、間質性肺疾患を含む肺臓炎の発現率は 6.0%（157/2626 例）であった。グレード 2、3 及び 4 の有害事象は、それぞれ 3.0%（78/2626 例）、1.0%（27/2626 例）及び 0.3%（8/2626 例）に発現した。4 例（0.2%）が死亡した。発現までの期間の中央値は 2.7 ヵ月（範囲: 0.1～56.8 ヵ月）であった。129 例（82.2%）で回復が認められ、回復までの期間の中央値は 6.1 週間（範囲: 0.1+～149.3+週間）であった。 *免疫に関連した肝毒性* イピリムマブは、免疫に関連した重度の肝毒性を伴う。イピリムマブ 3 mg/kg 単剤療法を受けた患者の 1%未満で致死的な肝不全が報告されている。 重症度を問わない AST 増加及び ALT 増加は、それぞれ 1%及び 2%に報告された。重度（グレード 3 又は 4）の AST 又は ALT 増加の報告はなかった。中等度から重度又は致死的（グレード 2～5）の免疫に関連した肝毒性が発現するまでの期間は、投与開始から 3～9 週間であった。治験実施計画書に規定された管理ガイドラインでは、回復までの期間は 0.7～2 週間であった。臨床試験では、免疫に関連した肝毒性を発現した患者の肝生検で急性炎症のエビデンス（好中球、リンパ球、マクロファージ）が認められた。 推奨用量よりも高用量のイピリムマブをダカルバジンと併用投与した患者では、イピリムマブ 3 mg/kg 単剤投与患者よりも免疫に関連した肝毒性の発現頻度が高かった。 イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者では、肝機能検査値異常の発現率は 21.2%（556/2626 例）であった。グレード 2、3 及び 4 の有害事象は、それぞれ 5.0%（132/2626 例）、8.3%（218/2626 例）及び 1.3%（34/2626 例）に発現した。7 例（0.3%）が死亡した。発現までの期間の中央値は 1.5 ヵ月（範囲: 0.0～36.6 ヵ月）であった。482 例（87.0%）で回復が認められ、回復までの期間の中央値は 5.9 週間（範囲: 0.1～175.9+週間）であった。悪性黒色腫に対してイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併用投与した患者では、肝機能検査値異常の発現率は 30.1%で、グレード 2（6.9%）、グレード 3（15.8%）及びグレード 4（1.8%）であった。HCC に対してイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併

用投与した患者において、肝機能検査値異常の発現率は 34.3%であり、その内訳はグレード 2（8.4%）、グレード 3（14.2%）及びグレード 4（2.7%）であった。

免疫に関連した皮膚の副作用

イピリムマブは、免疫に関連すると考えられる重度の皮膚の副作用を伴う。致死的な中毒性表皮壊死融解症（SJS を含む）は、イピリムマブと gp100 の併用投与を受けた患者の 1%未満で報告されている（5.1 項参照）。イピリムマブの臨床試験及び市販後の使用において、好酸球増加と全身症状を伴う薬物反応（DRESS）が稀に報告されている。市販後に類天疱瘡の偶発的な症例が報告されている。

イピリムマブ 3 mg/kg 単剤療法群では、重症度を問わない発疹及びそう痒症がそれぞれ患者の 26%で報告された。イピリムマブによる発疹及びそう痒症は、主に軽度（グレード 1）又は中等度（グレード 2）であり、対症療法が有効であった。中等度から重度又は致死的（グレード 2～5）な皮膚の副作用が発現するまでの期間の中央値は、投与開始から 3 週間（範囲: 0.9～16 週間）であった。治験実施計画書に規定された管理ガイドラインにより、ほとんどの症例（87%）で回復が認められ、発現から回復までの期間の中央値は 5 週間（範囲: 0.6～29 週間）であった。

イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者では、発疹の発現率は 46.1%（1210/2626 例）であった。グレード 2、3 及び 4 の有害事象は、それぞれ 14.3%（375/2626 例）、4.6%（120/2626 例）及び 0.1%（3/2626 例）で報告された。発現までの期間の中央値は 0.7 ヵ月（範囲: 0.0～33.8 ヵ月）であった。843 例（70%）で回復が認められ、回復までの期間の中央値は 12.1 週間（範囲: 0.1～268.7+週間）であった。悪性黒色腫に対してイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併用投与した患者では、発疹の発現率は 65.2%であり、グレード 2（20.3%）及びグレード 3（7.8%）を含んでいた。

免疫に関連した神経反応

イピリムマブは、免疫に関連した重度の神経反応を伴う。イピリムマブ 3 mg/kg と gp100 を併用投与した患者の 1%未満で、致死的なギラン・バレー症候群が報告されている。重症筋無力症様症状は、臨床試験で高用量のイピリムマブを投与された患者の 1%未満においても報告されている。

免疫に関連した腎炎及び腎機能障害

イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者において、腎炎又は腎機能障害の発現率は 5.4%（141/2626 例）であった。グレード 2、3 及び 4 の有害事象は、それぞれ 2.0%（52/2626 例）、0.8%（21/2626 例）及び 0.4%（11/2626 例）で発現した。2 例（0.1%未満）が死亡した。発現までの期間の中央値は 2.6 ヵ月（範囲: 0.0～34.8 ヵ月）であった。110 例（78.0%）で回復が認められ、回復までの期間の中央値は 5.9 週間（範囲: 0.1～172.1+週間）であった。

免疫に関連した内分泌障害

イピリムマブ 3 mg/kg 単剤療法群では、重症度を問わない下垂体機能低下症が患者の 4%で報告された。重症度を問わない副腎機能不全、甲状腺機能亢進症及び甲状腺機能低下症がそれぞれ患者の 2%で報告された。重度（グレード 3 又は 4）の下垂体機能低下症の発現頻度は 3%であった。中等度から極めて重度（グレード 2～4）の免疫

に関連した内分泌障害が発現するまでの期間は、投与開始から 7 週間から約 20 週間であった。臨床試験で認められた免疫に関連した内分泌障害は、ホルモン補充療法により概ねコントロール可能であった。

イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者において、甲状腺障害の発現率は 23.2%（608/2626 例）であった。グレード 2 及び 3 の甲状腺障害がそれぞれ 12.7%（333/2626 例）及び 1.0%（27/2626 例）で報告された。グレード 2 及び 3 の下垂体炎（リンパ球性下垂体炎を含む）は、それぞれ 1.9%（49/2626 例）及び 1.5%（40/2626 例）で発現した。グレード 2 及び 3 の下垂体機能低下症はそれぞれ 0.6%（16/2626 例）及び 0.5%（13/2626 例）で発現した。グレード 2、3 及び 4 の副腎機能不全（続発性副腎皮質機能不全、急性副腎皮質機能不全、血中コルチコトロピン減少及び免疫介在性副腎機能不全を含む）は、それぞれ 2.7%（72/2626 例）、1.6%（43/2626 例）及び 0.2%（4/2626 例）で発現した。グレード 1、2、3 及び 4 の糖尿病（1 型糖尿病、糖尿病性ケトアシドーシスを含む）の発現率は、それぞれ 0.1%未満（1/2626 例）、0.3%（8/2626 例）、0.3%（7/2626 例）及び 0.2%（6/2626 例）であった。これらの内分泌障害の発現までの期間の中央値は、2.1 ヵ月（範囲: 0.0～28.1 ヵ月）であった。297 例（40.0%）で回復が認められた。回復までの期間は 0.3~257.1^{+}週間であった。

Infusion reaction

イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者において、過敏症/Infusion reaction の発現率は 4.5%（118/2626 例）であった。グレード 1、2、3 及び 4 の症例は、それぞれ 1.9%（49/2626 例）、2.4%（62/2626 例）、0.2%（6/2626 例）及び 0.1%未満（1/2626 例）で報告された。イピリムマブ 1 mg/kg とニボルマブ 3 mg/kg を併用投与した MPM 患者における過敏症/Infusion reaction の発現率は 12%であった。

免疫原性

第 2 相及び第 3 相臨床試験でイピリムマブの投与を受けた進行性悪性黒色腫患者のうち、抗イピリムマブ抗体が発現した患者は 2%未満であった。注入に関連した又は注入に伴う過敏症又はアナフィラキシー反応は認められなかった。イピリムマブに対する中和抗体は検出されなかった。全体として、抗体産生と副作用との間に明らかな関連性は認められなかった。

イピリムマブとニボルマブの併用療法を受け、抗イピリムマブ抗体の有無について評価可能であった患者のうち、抗イピリムマブ抗体の発現率は 6.3～13.7%の範囲であった。イピリムマブに対する中和抗体は 0～0.4%であった。イピリムマブとニボルマブ及び化学療法の併用療法を受け、抗イピリムマブ抗体又はイピリムマブに対する中和抗体の有無について評価可能であった患者のうち、抗イピリムマブ抗体の発現率は 7.5%、イピリムマブに対する中和抗体の発現率は 1.6%であった。抗ニボルマブ抗体の有無が評価可能であった患者のうち、抗ニボルマブ抗体の発現率は、ニボルマブ 3 mg/kg 及びイピリムマブ 1 mg/kg の 3 週間間隔投与で 26%、ニボルマブ 3 mg/kg の 2 週間間隔投与及びイピリムマブ 1 mg/kg の 6 週間間隔投与で 24.9%、ニボルマブ 1 mg/kg 及びイピリムマブ 3 mg/kg の 3 週間間隔投与で 37.8%、ニボルマブ 360 mg の 3 週間間隔投与とイピリムマブ 1 mg/kg の 6 週間間隔投与及び化学療法の併用で 33.8%であった。ニボルマブに対する中和抗体の発現率は、ニボルマブ 3 mg/kg 及びイピリムマブ 1 mg/kg の 3 週間間隔投与で 0.8%、ニボルマブ 3 mg/kg の 2 週間間隔投与及びイピリムマブ 1 mg/kg の 6 週間間隔投与で 1.5%、ニボルマブ 1 mg/kg 及びイピ

リムマブ 3 mg/kg の 3 週間間隔投与で 4.6%、ニボルマブ 360 mg の 3 週間間隔投与とイピリムマブ 1 mg/kg の 6 週間間隔投与及び化学療法の併用で 2.6%であった。

ニボルマブと併用投与したとき、抗イピリムマブ抗体の存在下でもイピリムマブの CL は変化せず、毒性プロファイルの変化は認められなかった。

臨床検査値異常

イピリムマブとニボルマブの併用療法（化学療法の併用又は非併用）を受けた患者において、ベースラインからグレード 3 又は 4 の臨床検査値異常の悪化が見られた患者の割合は、貧血が 4.8%、血小板減少症が 1.8%、白血球減少症が 2.2%、リンパ球減少症が 6.9%、好中球減少症が 3.3%、アルカリホスファターゼ増加が 2.7%、AST 増加が 9.8%、ALT 増加が 9.3%、総ビリルビン増加が 2.3%、クレアチニン増加が 1.8%、低アルブミン血症が 1.4%、高血糖が 7.1%、低血糖が 0.7%、アミラーゼ増加が 7.8%、リパーゼ増加が 16.3%、低カルシウム血症が 0.8%、高ナトリウム血症が 0.2%、高カルシウム血症が 0.8%、高カリウム血症が 2.0%、高マグネシウム血症が 0.8%、低マグネシウム血症が 0.4%、低カリウム血症が 3.0%、低ナトリウム血症が 8.7%であった。

悪性黒色腫に対してイピリムマブ 3 mg/kg とニボルマブ 1 mg/kg を併用投与した患者では、ベースラインからグレード 3 又は 4 の ALT 増加が見られた患者の割合が高かった（15.3%）。

小児集団

イピリムマブ単剤療法

12 歳以上の青少年における新たな副作用は報告されなかった。

CA184-070 試験において、イピリムマブ 3 mg/kg を投与した 12 歳以上の患者 1 例では、グレード 3 以上の免疫に関連した副作用（irAR）は報告されなかった。5 mg/kg 群の 8 例中 2 例（25.0%）、10 mg/kg 群の 9 例中 1 例（11.1%）において、グレード 3～4 の事象が報告された。死亡に至った事象はなかった。irAR の種類は成人のものと一致しており、すべての群で最も多く報告された irAR は胃腸（0［3 mg/kg］、62.5%［5 mg/kg］、44.4%［10 mg/kg］）、肝機能（0［3 mg/kg］、75.0%［5 mg/kg］、33.3%［10 mg/kg］）及び皮膚（0［3 mg/kg］、25.0%［5 mg/kg］、33.3%［10 mg/kg］）の事象カテゴリーであった。本試験では、新規又は予測できない irAR は認められなかった。成人と小児集団で報告された irAR のスペクトルに明らかな差は認められなかった。

CA184-178 試験では、新規又は予測できない irAR は認められず、認められた irAR の発現頻度、程度及び器官部位は、成人を対象とした試験で報告されているものと同様であった。10 mg/kg 群の 2 例に、治験期間中にグレード 1 及び 3 の内分泌 irAR である高血糖が発現した。その他の内分泌異常は報告されなかった。

イピリムマブとニボルマブの併用

CA209-070 試験において、進行性悪性黒色腫を含む再発又は難治性の固形又は血液腫瘍を有する 1 歳以上 18 歳未満の小児患者 33 例（12 歳以上 18 歳未満の患者 20 例を含む）を対象に、イピリムマブ（1 mg/kg、3 週間間隔投与）とニボルマブ（最初の 4 回

	は 1 mg/kg 又は 3 mg/kg 投与、その後はニボルマブ単剤 3 mg/kg を 2 週間間隔で投与）の併用療法の安全性を評価した。小児患者における安全性プロファイルは、イピリムマブとニボルマブを併用投与した成人患者で認められた安全性プロファイルと概ね同様であった。新たな安全性シグナルは認められなかった。 イピリムマブとニボルマブの併用療法で最も多く認められた副作用（小児患者の 20%以上で報告）は、疲労（33.3%）及び斑状丘疹状皮疹（21.2%）であった。イピリムマブとニボルマブの併用療法で報告された副作用の大部分は、グレード 1 又は 2 であった。10 例（30%）に 1 つ以上のグレード 3 又は 4 の副作用が発現した。 高グレードの原発性中枢神経系（CNS）悪性腫瘍を有する小児患者 74 例を対象とした CA209-908 試験（5.1 項参照）では、各適応症の成人を対象とした試験で得られたデータと比較して、新たな安全性シグナルは認められなかった。 <u>高齢者</u> MPM 患者では、イピリムマブとニボルマブを併用投与したすべての患者（それぞれ 54%及び 28%）と比較して、75 歳以上の患者（それぞれ 68%及び 35%）で重篤な副作用の発現率及び副作用による中止率が高かった。75 歳以上の dMMR 又は MSI-H を有する CRC 患者のデータは限られている（5.1 項参照）。HCC 患者では、イピリムマブとニボルマブを併用投与したすべての患者（それぞれ 53%及び 27%）と比較して、75 歳以上の患者（それぞれ 67%及び 35%）で重篤な副作用の発現率及び副作用による中止率が高かった。 <u>本剤との関連性が疑われる副作用の報告</u> 医薬品の承認後に、医薬品との関連性が疑われる副作用を報告することは重要である。これにより医薬品のベネフィットとリスクのバランスを継続的にモニタリングすることができる。医療従事者は、付録 V に記載されている国内報告システムを介して、本剤との関連性が疑われる副作用を報告することが求められる。
薬物相互作用	イピリムマブはヒトモノクローナル抗体であり、チトクローム P450（CYP）酵素及び他の薬物代謝酵素によって代謝されない。 治療歴のない進行性悪性黒色腫の成人患者を対象に、イピリムマブを単剤投与、及び化学療法（ダカルバジン又はパクリタキセル/カルボプラチン）との併用投与における薬物相互作用試験を実施し、CYP アイソザイム（特に CYP1A2、CYP2E1、CYP2C8 及び CYP3A4）との相互作用を評価した。イピリムマブとパクリタキセル/カルボプラチン、ダカルバジン又はその代謝物である 5-アミノイミダゾール 4-カルボキサミド（AIC）との間に、臨床的に重要な薬物動態学的薬物相互作用は認められなかった。 <u>その他の相互作用</u> <u>*コルチコステロイド*</u> イピリムマブの薬力学的活性及び有効性に影響を及ぼす可能性があるため、イピリムマブ投与開始前のベースライン時における全身性コルチコステロイドの使用は避けること。しかしながら、イピリムマブの投与開始後は、免疫に関連した副作用の治療を行うために、全身性コルチコステロイド又はその他の免疫抑制剤を使用することがで

	きる。イピリムマブ投与開始後の全身性コルチコステロイドの使用は、イピリムマブの有効性を損なうことはないと考えられる。 *抗凝固薬* 抗凝固薬の使用は、消化管出血のリスクを増加させることが知られている。消化管出血はイピリムマブの副作用であるため（4.8 項参照）、抗凝固療法との併用が必要な患者は注意深く観察すること。
特定の集団における使用	小児集団 12 歳未満の小児における YERVOY 単剤療法の安全性及び有効性は確立されていない。利用可能なデータは非常に限られている。12 歳未満の小児には YERVOY を投与しないこと。 悪性黒色腫を有する 12 歳以上の青年患者を除き、18 歳未満の小児患者における YERVOY とニボルマブの併用療法の安全性及び有効性は確立されていない。現在得られているデータを 4.2 項、4.8 項、5.1 項及び 5.2 項に記載している。 高齢者 全体として、高齢患者（65 歳以上）と若年患者（65 歳未満）の間で安全性又は有効性に差は認められなかった。一次治療を受けた 75 歳以上の RCC 患者のデータは非常に限られているため、この患者集団について結論を導くことはできない（5.1 項参照）。この患者集団における特別な用量調節は不要である（5.1 項参照）。 腎機能障害 腎機能障害患者における YERVOY の安全性及び有効性は検討されていない。母集団薬物動態解析の結果に基づき、軽度から中等度の腎機能障害患者における特別な用量調節は不要である（5.2 項参照）。 肝機能障害 肝機能障害患者における YERVOY の安全性及び有効性は検討されていない。母集団薬物動態解析の結果に基づき、軽度の肝機能障患者における特別な用量調節は不要である（5.2 項参照）。ベースライン時のトランスアミナーゼ値が ULN の 5 倍以上又はビリルビン値が ULN の 3 倍超の患者には、YERVOY を慎重に投与しなければならない（5.1 項参照）。 妊娠 妊婦におけるイピリムマブの使用に関するデータはない。動物を用いた生殖発生毒性試験では、生殖毒性が認められている（5.3 項参照）。ヒト IgG1 は胎盤関門を通過する。発育中の胎児に対する本剤投与の潜在的リスクは不明である。臨床上の有益性が潜在的リスクを上回ると判断されない限り、妊娠中又は有効な避妊法を使用していない妊娠可能な女性への YERVOY の投与は推奨されない。 授乳 妊娠中にイピリムマブを投与されたカニクイザルの乳汁中に、極めて低い濃度のイピリムマブが存在していたことが示されている。イピリムマブがヒト乳汁中に移行するかどうかは不明である。一般に、IgG のヒト乳汁中への分泌は限定的であり、IgG の

	経口バイオアベイラビリティは低い。乳児への顕著な全身曝露は予測されず、授乳中の新生児/乳児に対する影響は予想されない。しかし、授乳中の乳児に副作用が発現する可能性があるため、授乳を中止するか、YERVOY の投与を中止するかは、乳児に対する授乳のベネフィットと女性に対する YERVOY の治療のベネフィットを考慮して決定しなければならない。 受胎能 受胎能に対するイピリムマブの影響を評価する試験は実施されていない。したがって、イピリムマブが男性及び女性の受胎能に及ぼす影響は不明である。
過量投与	イピリムマブの最大耐量は決定されていない。臨床試験では、20 mg/kg までの用量で明らかな毒性作用は認められなかった。 過量投与の場合は、副作用の徴候又は症状について患者を注意深くモニタリングし、適切な対症療法を開始すること。
添付文書の改訂年月日	2025 年 2 月

14 臨床試験

dMMR 又は MSI-H を有する結腸・直腸癌

治療歴のない dMMR 又は MSI-H を有する転移性 CRC 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と化学療法を比較する非盲検試験

腫瘍の MSI-H 又は dMMR の状態が確認されている切除不能又は転移性 CRC の一次治療として、イピリムマブ 1 mg/kg とニボルマブ 240 mg を 3 週間間隔で最大 4 回併用投与した後、ニボルマブ 480 mg を 4 週間間隔で単剤投与したときの安全性及び有効性を、無作為化、多群、第 3 相、非盲検試験（CA209-8HW）で評価した。投与群には、ニボルマブの単剤療法、ニボルマブとイピリムマブの併用療法、又は治験責任医師が選択した化学療法が含まれる。MSI-H 又は dMMR の腫瘍の状態は、PCR、NGS 又は IHC 法を用いた現地の標準的な手法に従って判定された。PCR（Idylla MSI）検査を用いた MSI-H の状態、及び IHC（Omnis MMR）検査を用いた dMMR の状態に関する中央判定は、各治験実施医療機関での MSI-H/dMMR の状態判定に用いた患者の腫瘍検体を用いてレトロスペクティブに実施した。いずれかの中央検査機関の検査により MSI-H/dMMR の状態が確認された患者を、主要有効性解析対象集団とした。症候性の脳転移を有する患者、活動性の自己免疫疾患を有する患者、全身性コルチコステロイド又は免疫抑制剤を使用している患者、又はチェックポイント阻害剤の投与を受けたことがある患者は、本試験から除外した。無作為化は、腫瘍の部位（右 vs 左）により層別化した。化学療法群に無作為化された患者は、BICR によって病勢進行が評価された時点で、イピリムマブ及びニボルマブの併用療法が実施された。

ニボルマブとイピリムマブの併用療法に 202 例、化学療法に 101 例の、計 303 例の治療歴のない転移性患者が無作為に割り付けられた。このうち 255 例は中央測定機関で MSI-H/dMMR が確認されており、171 例はイピリムマブとニボルマブの併用療法群、84 例は化学療法群に割り付けられた。イピリムマブとニボルマブ併用療法群の患者には、イピリムマブ 1 mg/kg とニボルマブ 240 mg を 3 週間間隔で併用投与し、最大 4 回投与した後、ニボルマブ 480 mg 単剤を 4 週間間隔で投与した。化学療法群の患者には、以下を投与した：mFOLFOX6（オキサリプラチン、ロイコボリン、フルオロウラシル）に、ベバシズマブ又はセツキシマブを併用又は非併用で投与する：オキサリプラチン 85 mg/m^2、ロイコボリン 400 mg/m^2 及びフルオロウラシル 400 mg/m^2 をボーラス投与後、フルオロウラシル 2400 mg/m^2 を 46 時間かけて 2 週間ごとに投与する。mFOLFOX6 投与前にベバシズマブ 5 mg/kg 又はセツキシマブ 500 mg/m^2 を 2 週間ごとに投与するか、又は FOLFIRI（イリノテカン、ロイコボリン、フルオロウラシル）に、ベバシズマブ又はセツ

キシマブを併用又は非併用で投与する：イリノテカン 180 mg/m^2、ロイコボリン 400 mg/m^2、フルオロウラシル 400 mg/m^2 をボーラス投与後、フルオロウラシル 2400 mg/m^2 を 46 時間かけて 2 週間ごとに投与する。FOLFIRI 投与前にベバシズマブ 5 mg/kg 又はセツキシマブ 500 mg/m^2 を 2 週間ごとに投与する。治療は、病勢進行、許容できない毒性が認められるまで、又はイピリムマブとニボルマブの併用療法では最長 24 ヵ月まで継続した。イピリムマブに起因する副作用により併用療法を中止した患者は、ニボルマブの単剤投与を継続することが認められた。RECIST v.1.1 に基づく腫瘍評価は、最初の 24 週間は 6 週間ごと、その後 96 週目までは 8 週間ごと、その後 146 週目までは 16 週間ごと、その後は 24 週間ごとに実施した。

無作為化された治療歴のない転移性疾患を有する全患者のベースライン時の特性は以下の通りであった：年齢の中央値が 63 歳（範囲: 21～87 歳）、65 歳以上が 46%、75 歳以上が 18%であった。46%が男性、86%が白人であった。ベースライン時の ECOG パフォーマンスステータスは 0（54%）及び 1 以上（46%）であった。腫瘍の位置は、68%が右側、32%が左側であった。また、状態が確認されていた 223 例のうち 39 例でリンチ症候群が判明した。中央測定機関で MSI-H/dMMR が確認された治療歴のない転移性疾患患者のベースライン特性は、無作為化されたすべての治療歴のない患者と一致していた。化学療法群に無作為化された 101 例のうち、88 例が治験実施計画書に従って化学療法を受け、その内訳はオキサリプラチンを含むレジメン（58%）及びイリノテカンを含むレジメン（42%）であった。さらに、66 例がベバシズマブ（64%）又はセツキシマブ（11%）のいずれかの分子標的薬の投与を受けた。

本試験における有効性の主要評価項目は、RECIST v1.1 に基づく BICR 判定による PFS であった。その他の有効性評価項目は、BICR の評価による ORR、OS 及び奏効期間とした。

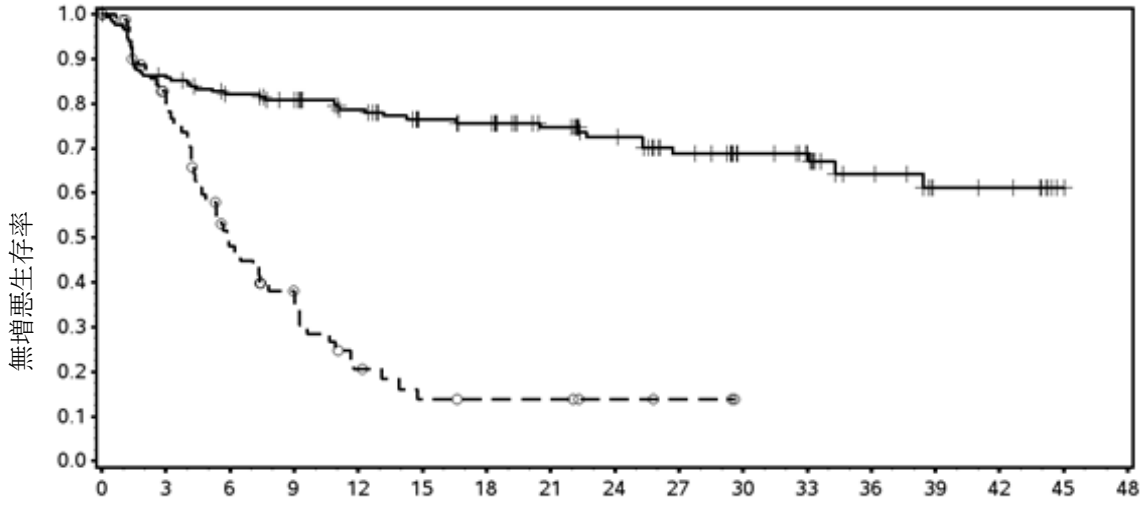
本試験は、計画された中間解析時点で主要評価項目を達成し、中央測定機関で確認された MSI-H/dMMR を有する患者において、イピリムマブ及びニボルマブの併用療法群は、化学療法群と比較して統計学的に有意な PFS の改善が認められた。BICR 判定による PFS の結果を表 19 及び図 11 に示す。本中間解析時点では、ニボルマブ単剤療法群のデータを含むその他の評価項目については、試験の階層により評価されていない。

表 19: MSI-H/dMMR が中央判定で確認されている CRC 患者の一次治療における有効性の結果（CA209-8HW）[a]

	イピリムマブ＋ニボルマブ（n=171）	化学療法（n=84）
無増悪生存期間		
事象	48 例（28%）	52 例（62%）
ハザード比	0.21	
95% CI	（0.14、0.32）	
p 値 [b]	0.0001 未満	
中央値（95% CI）（ヵ月）	NR（38.4、NR）	5.9（4.4、7.8）

[a] 追跡調査期間の中央値は 31.5 ヵ月（範囲: 6.1～48.4 ヵ月）。
[b] 層別両側 Log-rank 検定に基づく。

図 11: MSI-H/dMMR が中央判定で確認されている CRC 患者の一次治療における PFS の Kaplan-Meier 曲線（CA209-8HW）



リスクのある被験者数

ニボルマブ＋イピリムマブ

171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0

化学療法

84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

----+--- ニボルマブ＋イピリムマブ（事象: 48/171）、中央値及び 95% CI: N.A.（38.44、N.A.）

----○--- 化学療法（事象: 52/84）、中央値及び 95% CI: 5.85（4.37、7.79）

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