キイトルーダ点滴静注 100mg
に関する資料

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MSD 株式会社

CTD 第 1 部

1.5　起原又は発見の経緯及び開発の経緯

MSD 株式会社

1.5　起原又は発見の経緯及び開発の経緯

当該内容については、[2.5.1 項]参照。

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CTD 第 1 部

1.6　外国における使用状況等に関する資料

MSD 株式会社

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表一覧

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1.6　外国における使用状況等に関する資料

1.6.1　外国における使用状況等

外国における本剤の使用状況は[表 1.6.1-1]のとおり。

2024年7月31日現在、本剤と同時化学放射線療法の併用療法及び同時化学放射線療法の単独療法における局所進行子宮頸癌の治療薬として、KEYNOTE-A18試験に基づき米国を含む15の国又は地域で承認されている。EU では2023年10月に承認申請し、現在審査中である。

表 1.6.1-1　外国における本剤の使用状況

本剤が最初に承認された年月	2014年9月（米国、悪性黒色腫）
本剤の欧米等6ヵ国（米・英・独・仏・加・豪）の承認状況	すべて承認取得済み。

1.6.2　外国の添付文書

1.6.2.1　外国の添付文書の概要（和訳）

1.6.2.1.1　米国添付文書の概要（和訳）

米国添付文書の概要を以下に示す。概要の項目番号は原文の項目番号にあわせた。

販売名／販売会社名

KEYTRUDA®／Merck Sharp & Dohme LLC

効能・効果

1　効能・効果

1.1　悪性黒色腫

KEYTRUDA®は、切除不能又は転移性の悪性黒色腫の治療を適応とする。

KEYTRUDA は、成人及び小児（12歳以上）の IIB 期、IIC 期又は III 期の悪性黒色腫に対する完全切除後の術後補助療法を適応とする。

1.2　非小細胞肺癌

KEYTRUDA は、EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性ではない、転移性の非扁平上皮非小細胞肺癌に対するペメトレキセド及びプラチナ製剤化学療法との併用による一次治療を適応とする。

KEYTRUDA は、転移性の扁平上皮非小細胞肺癌に対するカルボプラチン及びパクリタキセル又はパクリタキセル（アルブミン懸濁型）（nab-パクリタキセル）との併用による一次治療を適応とする。

KEYTRUDA は、FDA が承認した診断薬［用法・用量（2.1）参照］により腫瘍細胞に PD-L1発現［Tumor Proportion Score（腫瘍細胞のうち PD-L1発現陽性細胞の割合）: TPS≥1%］が確認され、EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性ではない非小細胞肺癌に対する単独投与による一次治療を適応とする［用法・用量（2.1）参照］。さらに、以下のいずれかに該当すること。

- 外科的切除及び根治的化学放射線療法が不適応の III 期の非小細胞肺癌
- 転移性の非小細胞肺癌

KEYTRUDA は、プラチナ製剤併用化学療法による治療中及び治療後に疾患進行が認められ、FDA が承認した診断薬により腫瘍細胞に PD-L1発現陽性（TPS≥1%）が確認された転移性の非小細胞肺癌に対する単独投与を適応とする［用法・用量（2.1）参照］。EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性の患者については、KEYTRUDA の投与前にこれらの変異に対して FDA が承認した治療を受けたものの疾患進行が認められた患者とする。

KEYTRUDA とプラチナ製剤化学療法との併用による術前補助療法及びその後の KEYTRUDA の単独投与による術後薬物療法は、切除可能（腫瘍≥4 cm 又はリンパ節転移陽性）な非小細胞肺癌の治療を適応とする。

KEYTRUDA は、外科的切除及びプラチナ製剤併用化学療法後の IB 期（T2a≥4 cm）、II 期、又は IIIA 期の成人の非小細胞肺癌に対する単独投与による術後補助療法を適応とする。

1.3　頭頸部扁平上皮癌

KEYTRUDA は、転移性又は切除不能の再発頭頸部扁平上皮癌のプラチナ製剤及びフルオロウラシルとの併用による一次治療を適応とする。

KEYTRUDA は、FDA が承認した診断薬により腫瘍細胞に PD-L1発現陽性［Combined Positive Score（CPS）≥1］が確認された転移性又は切除不能の再発頭頸部扁平上皮癌の単独投与による一次治療を適応とする［用法・用量（2.1）参照］。

KEYTRUDA は、プラチナ製剤併用化学療法による治療中及び治療後に疾患進行が認められた再発性又は転移性の頭頸部扁平上皮癌の単独投与による治療を適応とする。

1.4　古典的ホジキンリンパ腫

KEYTRUDA は、成人の再発性又は難治性古典的ホジキンリンパ腫（cHL）の治療を適応とする。

KEYTRUDA は、小児の難治性古典的ホジキンリンパ腫又は2レジメン以上の治療後に再発した古典的ホジキンリンパ腫の治療を適応とする。

1.5　原発性縦隔大細胞型 B 細胞リンパ腫

KEYTRUDA は、成人及び小児の難治性又は2レジメン以上の治療後に再発した原発性縦隔大細胞型 B 細胞リンパ腫（PMBCL）の治療を適応とする。

使用制限：緊急の細胞減少療法を要する原発性縦隔大細胞型 B 細胞リンパ腫に対して、KEYTRUDA を投与することは推奨されない。

1.6　尿路上皮癌

KEYTRUDA は、成人の局所進行性又は転移性の尿路上皮癌に対するエンホルツマブベドチンとの併用による治療を適応とする。

KEYTRUDA は、以下のいずれかに該当する局所進行性又は転移性の尿路上皮癌の単独投与による治療を適応とする。

- プラチナ製剤併用化学療法に不耐容、又は
- プラチナ製剤併用化学療法による治療中若しくは治療後に疾患進行が認められた、又はプラチナ製剤併用化学療法による術前若しくは術後補助療法から12ヵ月以内に疾患進行が認められた

KEYTRUDA は、乳頭状腫瘍の有無によらない、上皮内癌（CIS）を有する、カルメット・ゲラン桿菌（BCG）療法不応性の高リスク筋層非浸潤性膀胱癌（NMIBC）における、根治的膀胱全摘除術が不適格又は根治的膀胱全摘除術を希望しない患者の単独投与による治療を適応とする。

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1.7　MSI-High 又は MMR 欠損の癌

KEYTRUDA は、前治療後に進行し、代替治療が十分に期待できない成人及び小児の切除不能又は転移性の、FDA が承認した診断薬により確認された MSI-High 又は MMR 欠損固形がんの治療を適応とする［用法・用量（2.1）参照］。

1.8　MSI-High 又は MMR 欠損の結腸・直腸癌

KEYTRUDA は、切除不能又は転移性の、FDA が承認した診断薬により確認された MSI-High 又は MMR 欠損の結腸・直腸癌の治療を適応とする［用法・用量（2.1）参照］。

1.9　胃癌

KEYTRUDA は、FDA が承認した診断薬により腫瘍細胞に PD-L1発現陽性（CPS≥1）が確認された、局所進行の切除不能又は転移性の HER2陽性胃腺癌又は食道胃接合部（GEJ）腺癌の成人患者に対するトラスツズマブ、フッ化ピリミジン系製剤及びプラチナ製剤併用化学療法との併用による一次治療を適応とする［用法・用量（2.1）参照］。

本適応は、奏効率及び持続する奏効に基づき、迅速承認を取得した［臨床試験（14.9）参照］。本適応の承認継続は、検証試験での臨床効果の確認及び陳述が必要となる場合がある。

KEYTRUDA は、局所進行の切除不能又は転移性の HER2陰性胃腺癌又は食道胃接合部（GEJ）腺癌の成人患者に対するフッ化ピリミジン系製剤及びプラチナ製剤併用化学療法との併用による一次治療を適応とする。

1.10　食道癌

KEYTRUDA は、外科的切除及び根治的化学放射線療法が不適応の、局所進行又は転移性の食道癌又は食道胃接合部（GEJ）癌（腫瘍の中心が食道胃接合部の上1～5 cm にあるもの）に対して、以下のいずれかでの治療を適応とする。

- プラチナ製剤及びフッ化ピリミジン系製剤併用化学療法との併用投与、又は
- FDA が承認した診断薬により PD-L1発現陽性（CPS≥10）が確認された、1レジメン以上の全身性の治療歴のある扁平上皮癌患者に対する単独投与［用法・用量（2.1）参照］

1.11　子宮頸癌

KEYTRUDA は、国際産婦人科連合（FIGO）2014進行期分類の IIIーIVA 期子宮頸癌患者に対する化学放射線療法（CRT）との併用治療を適応とする。

KEYTRUDA は、FDA が承認した診断薬により腫瘍細胞に PD-L1発現陽性（CPS≥1）が確認された、持続、再発又は転移性の子宮頸癌患者に対するベバシズマブ併用又は非併用での化学療法との併用治療を適応とする［用法・用量（2.1）参照］。

KEYTRUDA は、化学療法による治療中又は治療後に疾患進行が認められ、FDA が承認した診断薬により腫瘍細胞に PD-L1発現陽性（CPS≥1）が確認された、再発又は転移性の子宮頸癌の単独

投与による治療を適応とする［用法・用量（2.1）参照］。

1.12　肝細胞癌

KEYTRUDA は、前治療として PD-1/PD-L1療法以外の全身療法レジメンを受けた B 型肝炎による肝細胞癌（HCC）患者の治療を適応とする。

1.13　胆道癌

KEYTRUDA は、局所進行の切除不能又は転移性の胆道癌患者に対するゲムシタビン及びシスプラチンとの併用による治療を適応とする。

1.14　メルケル細胞癌

KEYTRUDA は、成人及び小児の再発した局所進行性又は転移性のメルケル細胞癌の治療を適応とする。

1.15　腎細胞癌

KEYTRUDA は、成人の進行性腎細胞癌のアキシチニブとの併用による一次治療を適応とする。

KEYTRUDA は、成人の進行性腎細胞癌のレンバチニブとの併用による一次治療を適応とする。

KEYTRUDA は、腎摘出後又は腎摘出及び転移巣切除後に中程度から高度又は高度の再発リスクを有する進行性腎細胞癌の術後補助療法を適応とする［臨床試験（14.15）参照］。

1.16　子宮体癌

KEYTRUDA は、成人の原発性進行又は再発子宮体癌に対するカルボプラチン及びパクリタキセルとの併用投与、及びそれに続く単独投与による治療を適応とする。

KEYTRUDA は、これまでの全身性の前治療後に疾患進行が認められ、根治的切除術又は放射線療法が不適応の、FDA が承認した診断薬により pMMR が確認された又は MSI-High を有さない成人進行子宮体癌に対するレンバチニブとの併用による治療を適応とする［用法・用量（2.1）参照］。

KEYTRUDA は、これまでの全身性の前治療後に疾患進行が認められ、根治的切除術又は放射線療法が不適応であり、FDA が承認した診断薬により MSI-High 又は MMR 欠損を有すると確認された、成人の進行子宮体癌の単独投与による治療を適応とする［用法・用量（2.1）参照］。

1.17　腫瘍遺伝子変異量高値の癌（TMB-High 癌）

KEYTRUDA は、前治療後に進行し、代替治療が十分に期待できず、FDA が承認した診断薬により腫瘍遺伝子変異量高値（TMB-High）［10変異／メガベース（mut/Mb）以上］であることが確認された、成人及び小児の切除不能又は転移性の固形がんの治療を適応とする［用法・用量（2.1）参照］。

本適応は、奏効率及び持続する奏効に基づき、迅速承認を取得した［臨床試験（14.17）参照］。本適応の承認継続は、検証試験での臨床効果の確認及び陳述が必要となる場合がある。

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使用制限：小児の TMB-High の中枢神経系癌患者における KEYTRUDA の安全性及び有効性は確立されていない。

1.18　皮膚扁平上皮癌

KEYTRUDA は、手術又は放射線療法では治癒不能の再発又は転移性の皮膚扁平上皮癌（cSCC）又は局所進行性の cSCC の治療を適応とする。

1.19　トリプルネガティブ乳癌

KEYTRUDA は、高リスク早期トリプルネガティブ乳癌患者に対する術前補助療法として化学療法との併用投与、及び術後補助療法として単独投与による継続治療を適応とする。

KEYTRUDA は、FDA が承認した診断薬により腫瘍細胞に PD-L1発現陽性［Combined Positive Score（CPS）≥10］が確認された、局所再発性・切除不能又は転移性のトリプルネガティブ乳癌患者に対する化学療法との併用治療を適応とする［用法・用量（2.1）参照］。

1.20　成人の古典的ホジキンリンパ腫及び成人の原発性縦隔大細胞型 B 細胞リンパ腫：400 mg 6週間間隔投与レジメン

KEYTRUDA は、成人の古典的ホジキンリンパ腫及び成人の原発性縦隔大細胞型 B 細胞リンパ腫に対する追加の推奨用量として400 mg の6週間間隔投与を適応とする［効能・効果（1.4、1.5）、用法・用量（2.2）参照］。本適応は、薬物動態学的データ、曝露と有効性の関係及び曝露と安全性の関係に基づき、迅速承認を取得した［臨床薬理試験（12.2）、臨床試験（14.20）参照］。本適応の承認継続は、検証試験での臨床効果の確認及び陳述が必要となる場合がある。

用法・用量

2　　用法・用量

2.1　　患者選択

患者選択を目的とした FDA が承認した診断薬の情報は、以下を参照：
http://www.fda.gov/CompanionDiagnostics

単独投与に対する患者選択

KEYTRUDA の単独投与では、PD-L1発現の有無に基づき以下の患者を選択する。

- 外科的切除及び根治的化学放射線療法が不適応の III 期の非小細胞肺癌［臨床試験（14.2）参照］
- 転移性の非小細胞肺癌［臨床試験（14.2）参照］
- 転移性又は切除不能の再発頭頸部扁平上皮癌の一次治療［臨床試験（14.3）参照］
- 既治療の局所進行再発又は転移性の食道癌［臨床試験（14.10）参照］
- 化学療法による治療中又は治療後に疾患進行が認められた再発又は転移性の子宮頸癌［臨床試験（14.11）参照］

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MSI-High 又は MMR 欠損の癌を適応とする場合、KEYTRUDA の単独投与では、腫瘍検体の MSI-High 又は MMR 欠損の状態に基づき患者を選択する［臨床試験（14.7、14.8）参照］。

TMB-High 癌を適応とする場合、KEYTRUDA の単独投与では、腫瘍検体の TMB-High の状態に基づき患者を選択する［臨床試験（14.17）参照］。

テモゾロミドによる化学療法中に高悪性度神経膠腫でサブクローナル dMMR 変異及びマイクロサテライト不安定性が生じる可能性があるため、高悪性度神経膠腫患者では、テモゾロミドによる化学療法を開始する前に採取した原発腫瘍検体を用いて、TMB-High、MSI-High 及び MMR 欠損を検査することが推奨される。

非結腸・直腸癌の固形がん患者における MSI-High 又は MMR 欠損に関する追加の患者選択情報

施設で用いる診断薬による検査と FDA が承認した診断薬による検査との間に不一致があるため、可能であれば、MSI-High 又は MMR 欠損の固形がん患者では FDA が承認した診断薬での MSI-High 又は MMR 欠損の状態を確認すること推奨される。確認のための MSI-High／MMR 欠損の診断薬が使用できない場合は、FDA が承認した診断薬で定められた TMB≥10 mut/Mb を用いて患者を選択する［臨床試験（14.7）参照］

<u>併用療法に対する患者選択</u>

KEYTRUDA と化学療法及びトラスツズマブとの併用投与では、PD-L1発現（CPS≥1）の有無に基づき局所進行の切除不能又は転移性の HER2陽性胃腺癌又は食道胃接合部（GEJ）腺癌の患者を選択する［臨床試験（14.9）参照］。

KEYTRUDA とベバシズマブ併用又は非併用での化学療法との併用投与では、PD-L1発現の有無に基づき持続、再発又は転移性の子宮頸癌患者を選択する［臨床試験（14.11）参照］。

pMMR である又は MSI-High を有さない進行子宮体癌を適応とする場合、レンバチニブとの併用投与では、腫瘍検体の MSI 又は MMR の状態に基づき患者を選択する［臨床試験（14.16）参照］。

KEYTRUDA と化学療法との併用投与では、PD-L1発現の有無に基づき局所再発性・切除不能又は転移性のトリプルネガティブ乳癌患者を選択する［臨床試験（14.19）参照］。

<u>患者の選択に関する追加情報</u>

現時点で、非 MSI-High の検出を目的として FDA が承認した診断薬を、KEYTRUDA とレンバチニブの併用療法に関する非 MSI-High の子宮体癌患者の選択に利用することはできない。［臨床試験（14.16）参照］。

2.2　推奨用量

表 1.6.2-1　推奨用量

適応	KEYTRUDA の推奨用量	投与期間
単独療法		

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成人の切除不能又は転移性の悪性黒色腫患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔*	疾患進行又は許容できない副作用の発現まで
成人の悪性黒色腫、非小細胞肺癌又は腎細胞癌患者の術後補助療法	200 mg を3週間間隔* 又は 400 mg を6週間間隔*	再発、許容できない副作用の発現又は最長12ヵ月まで
成人の非小細胞肺癌、頭頸部扁平上皮癌、古典的ホジキンリンパ腫、原発性縦隔大細胞型 B 細胞リンパ腫、局所進行又は転移性の尿路上皮癌、MSI-High 又は MMR 欠損の癌、MSI-High 又は MMR 欠損の結腸・直腸癌、MSI-High 又は MMR 欠損の子宮体癌、食道癌、子宮頸癌、肝細胞癌、メルケル細胞癌、腫瘍遺伝子変異量高値の癌又は皮膚扁平上皮癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔*	疾患進行、許容できない副作用の発現又は最長24ヵ月まで
成人の BCG 療法不応性の高リスク筋層非浸潤性膀胱癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔*	高リスク NMIBC の持続若しくは再発、疾患進行、許容できない副作用の発現又は最長24ヵ月まで
小児の古典的ホジキンリンパ腫、原発性縦隔大細胞型 B 細胞リンパ腫、MSI-High 又は MMR 欠損の癌、メルケル細胞癌又は腫瘍遺伝子変異量高値の癌患者	2 mg/kg（最大200 mg）を3週間間隔*	疾患進行、許容できない副作用の発現又は最長24ヵ月まで
小児（12歳以上）の悪性黒色腫患者の術後補助療法	2 mg/kg（最大200 mg）を3週間間隔*	再発、許容できない副作用の発現又は最長12ヵ月まで
併用療法†		
成人の切除可能な非小細胞肺癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA と化学療法を同日に併用投与する場合は、化学療法を投与する前に KEYTRUDA を投与する	化学療法と併用する術前補助療法として KEYTRUDA を12週間又は根治手術不適応な疾患進行若しくは許容できない副作用の発現まで投与、それに続く術後補助療法として KEYTRUDA を39週間単独投与若しくは疾患再発又は許容できない副作用の発現まで
成人の非小細胞肺癌、頭頸部扁平上皮癌、HER2陰性胃癌、食道癌又は胆道癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA と化学療法を同日に併用投与する場合は、化学療法を投与する前に KEYTRUDA を投与する	疾患進行、許容できない副作用の発現又は最長24ヵ月まで
成人の局所進行性又は転移性の尿路上皮癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔*	疾患進行、許容できない副作用の発現又は最長24ヵ月まで

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	KEYTRUDA とエンホルツマブベドチンを同日に併用投与する場合は、エンホルツマブベドチンを投与した後に KEYTRUDA を投与する	
成人の HER2陽性胃癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA とトラスツズマブ及び化学療法を同日に併用投与する場合は、トラスツズマブ及び化学療法を投与する前に KEYTRUDA を投与する	疾患進行、許容できない副作用の発現又は最長24ヵ月まで
成人の子宮頸癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA と化学放射線療法又はベバシズマブ併用若しくは非併用での化学療法を同日に行う場合は、化学放射線療法又はベバシズマブ併用若しくは非併用での化学療法を行う前に KEYTRUDA を投与する	疾患進行、許容できない副作用の発現又は KEYTRUDA を最長24ヵ月投与するまで
成人の腎細胞癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA とアキシチニブ5 mg 1日2回経口投与を併用投与する‡ 又は KEYTRUDA とレンバチニブ20 mg 1日1回経口投与を併用投与する	疾患進行、許容できない副作用の発現又は KEYTRUDA を最長24ヵ月投与するまで
成人の子宮体癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA とカルボプラチン及びパクリタキセルを同日に投与する場合は、カルボプラチン及びパクリタキセルの投与前に KEYTRUDA を投与する 又は KEYTRUDA とレンバチニブ20 mg 1日1回経口投与を併用投与する	疾患進行、許容できない副作用の発現又は KEYTRUDA を最長24ヵ月投与するまで
成人の高リスク早期トリプルネガティブ乳癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA と化学療法を同日に併用投与する場合は、化学療法を投与す	化学療法と併用する術前補助療法として KEYTRUDA を24週間投与（200 mg を3週間間隔で8回又は400 mg を6週間間隔で4回）又は疾患進行若しくは許容できない副作用の発現まで、それに続く術後補助療法として最長27週間まで KEYTRUDA を単独投与（200 mg を

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	る前に KEYTRUDA を投与する	3週間間隔で9回又は400 mg を6週間間隔で5回）又は再発若しくは許容できない副作用の発現まで§
成人の局所再発性・切除不能又は転移性トリプルネガティブ乳癌患者	200 mg を3週間間隔* 又は 400 mg を6週間間隔* KEYTRUDA と化学療法を同日に併用投与する場合は、化学療法を投与する前に KEYTRUDA を投与する	疾患進行、許容できない副作用の発現又は最長24ヵ月まで
* 30分間かけて点滴静注する † 必要に応じて、推奨用量について、KEYTRUDA と併用投与する薬剤の添付文書も参照のこと ‡ アキシチニブを KEYTRUDA と併用する場合、6週間以上投与後に、アキシチニブの初回用量5 mg からの増量を検討することができる § 疾患進行又は術前補助療法として化学療法と併用投与した KEYTRUDA に関連する許容できない副作用の発現が認められた患者には、術後補助療法として KEYTRUDA を単独投与しないこと		

2.3　用量調節

KEYTRUDA の減量は推奨されない。一般に、重度（Grade 3）の免疫関連の副作用が認められれば KEYTRUDA を休薬する。生命を脅かす（Grade 4）免疫関連の副作用、全身性の免疫抑制剤の投与を要する重度（Grade 3）の免疫関連の副作用の再発、又はステロイド投与開始後12週間以内に副腎皮質ホルモン剤の用量を10 mg／日以下（プレドニゾロン換算）に減量できない場合は KEYTRUDA 投与を中止する。

これらの一般的な指針と異なる管理を要する副作用が発現した場合の KEYTRUDA の用量調節について、[表 1.6.2-2]に要約する。

表 1.6.2-2　副作用に対して推奨される KEYTRUDA の用量調節

副作用	程度*	用量調節
免疫関連の副作用［警告及び使用上の注意（5.1）参照］		
肺臓炎	Grade 2	休薬†
	Grade 3又は4	中止
大腸炎	Grade 2又は3	休薬†
	Grade 4	中止
肝臓の腫瘍病変がみられない肝炎 アキシチニブとの併用投与を受けた患者の肝酵素増加については表1.6.2-3を参照	AST 又は ALT が基準値上限の3倍超8倍以下に増加 又は 総ビリルビンが基準値上限の1.5倍超3倍以下に増加	休薬†
	AST 又は ALT が基準値上限の8倍超に増加 又は 総ビリルビンが基準値上限の3倍超に増加	中止

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肝臓の腫瘍病変がみられる肝炎‡	ベースライン時に基準値上限の1倍超3倍以下であった場合の AST 又は ALT が基準値上限の5倍超及び10倍以下に増加 又は ベースライン時に基準値上限の3倍超5倍以下であった場合の AST 又は ALT が基準値上限の8倍超10倍以下に増加	休薬†
	ALT 又は AST が基準値上限の10倍超に増加 又は 総ビリルビンが基準値上限の3倍超に増加	中止
内分泌障害	Grade 3又は4	臨床的に安定するまで休薬又は程度に応じて中止
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	休薬†
	Grade 4の血中クレアチニン増加	中止
剥脱性皮膚疾患	SJS、TEN 又は DRESS が疑われる場合	休薬†
	SJS、TEN 又は DRESS が確定した場合	中止
心筋炎	Grade 2、3又は4	中止
神経毒性	Grade 2	休薬†
	Grade 3又は4	中止
血液毒性（古典的ホジキンリンパ腫又は原発性縦隔大細胞型 B 細胞リンパ腫患者）	Grade 4	Grade 1以下に回復するまで休薬
その他の副作用		
Infusion-related reaction［警告及び使用上の注意（5.2）参照］	Grade 1又は2	中断又は注入速度を下げる
	Grade 3又は4	中止

* 有害事象共通用語規準（CTCAE）v4.0に基づく。
† 副腎皮質ホルモン剤の漸減後、完全又は部分的に回復（Grade 1以下）した場合は、KEYTRUDA の使用を再開すること。ステロイド投与開始から12週間以内に完全若しくは部分的に回復しない又は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、KEYTRUDA の使用を中止する。
‡ ベースライン時に AST 又は ALT が基準値上限以下である場合、肝臓の腫瘍病変がみられない肝炎に対する勧告に基づき、KEYTRUDA を休薬又は中止すること。
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疹、SJS=スティーヴンス・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

次の表は、上記（KEYTRUDA）と異なる又は詳細な添付文書（併用投与薬）と異なる用量調節について示したものである。

表 1.6.2-3　アキシチニブとの併用投与後の副作用に対して推奨される KEYTRUDA の特別な用量調節

投与	副作用	程度	用量調節

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KEYTRUDA とアキシチニブとの併用投与	肝酵素増加*	ALT 又は AST が基準値上限の3倍以上10倍未満、かつ総ビリルビンが基準値上限の2倍未満	Grade 1以下に回復するまで KEYTRUDA とアキシチニブを休薬†
		ALT 又は AST が基準値上限の3倍超、かつ総ビリルビンが基準値上限の2倍以上 又は ALT 又は AST が基準値上限の10倍以上	KEYTRUDA とアキシチニブを中止

*　副腎皮質ホルモン剤の投与を考慮
†　有害事象共通用語規準（CTCAE）v4.0に基づく。回復後、いずれか一剤の再開又は両剤の順次再開を考慮する。アキシチニブの再開にあたっては、アキシチニブの添付文書に基づき減量を考慮する。
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、ULN = 基準値上限

レンバチニブとの併用投与後の副作用に対して推奨される KEYTRUDA の用量調節

レンバチニブと KEYTRUDA を併用投与する場合、いずれか一剤又は両剤の用量を調節する。[表 1.6.2-2]に示したように、KEYTRUDA を休薬又は中止する。レンバチニブの用量調節の詳細情報については、レンバチニブの添付文書を参照すること。

2.4　調製及び投与

点滴静注の準備

- 粒子状物質や変色がないか溶液を目視により確認する。溶液は澄明から僅かな乳白色、無色から微黄色を呈する。粒子が認められる場合は使用しないこと。
- 静脈内投与前に注射用溶液製剤を希釈する。
- バイアルから必要量を抜き取り、USP 0.9%生理食塩液又は USP 5%ブドウ糖注射液の点滴バッグに移す。希釈された溶液を振らずに静かに転倒混和する。最終的な希釈溶液は1～10 mg/mL の濃度となるようにする。
- 残液は廃棄すること。

希釈溶液の保存

本製品は保存料を含有していない。

100 mg/4 mL バイアルからの希釈溶液を以下のいずれかの方法で保存すること。

- 希釈溶液は室温で6時間まで保存できる。この時間には、希釈溶液の室温保存及び点滴投与時間を含む。
- 冷蔵条件下2°C～8°C（36°F～46°F）で、希釈溶液は96時間まで保存できる。冷蔵した場合は、希釈溶液を室温に戻してから使用すること。振らないこと。

室温下で6時間又は冷蔵下で96時間経過後は廃棄すること。

冷凍しないこと。

投与

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- 無菌の非発熱性の低タンパク結合の0.2～5 μm のインラインフィルター又はアドオンフィルターの点滴ラインで希釈溶液を30分間かけて静脈内投与する。
- 同じ点滴ラインで他の薬剤を併用投与しないこと。

剤型・含量

注射用溶液（澄明から僅かな乳白色、無色から微黄色）製剤100 mg/4 mL（25 mg/mL）バイアル

禁忌

なし

警告・使用上の注意

5　警告及び使用上の注意

5.1　重度及び死亡に至る免疫関連の副作用

KEYTRUDA は、プログラム細胞死1受容体（PD-1）又は PDーリガンド1（PD-L1）のいずれかに結合する一連の薬剤に属するモノクローナル抗体である。これは PD-1/PD-L1経路を遮断することにより免疫反応の阻害を解除するが、末梢性寛容を破綻させ免疫関連の副作用が誘導される可能性がある。警告及び使用上の注意に掲載する重要な免疫関連の副作用には、重度及び死亡に至る事象がすべて含まれているわけではない。

重度又は死亡に至る免疫関連の副作用は、いずれの器官系又は組織においても発現する可能性があり、2箇所以上の身体系に同時に影響を及ぼす可能性がある。免疫関連の副作用は、PD-1/PD-L1抗体の投与開始後いつでも起こりうる。通常は PD-1/PD-L1抗体の投与中に発現するが、投与の中止後に発現する可能性もある。

免疫関連の副作用を早期に特定・管理することは、PD-1/PD-L1抗体の安全な使用に不可欠である。免疫関連の副作用の根底にある臨床所見と思われる症状及び徴候を密接にモニタリングする。肝酵素、クレアチニン及び甲状腺機能について、ベースライン時及び投与期間中定期的に評価する。術前補助療法として KEYTRUDA を投与するトリプルネガティブ乳癌患者に対し、ベースライン時、術前及び臨床的必要性に応じて血中コルチゾールをモニタリングする。免疫関連の副作用が疑われる場合、感染症などほかの原因を除外するため適切な検査を開始する。適宜、専門医の受診を含め医療機関での管理を直ちに行う。

程度に応じて KEYTRUDA を休薬又は中止すること［用法・用量（2.3）参照］。一般に、KEYTRUDA の休薬又は中止を要する場合、Grade 1以下に改善するまで全身性副腎皮質ホルモン剤の投与（プレドニゾロン換算で1～2 mg/kg/日）を行う。Grade 1以下に改善した時点で副腎皮質ホルモン剤の漸減を開始し、1ヵ月以上これを継続する。副腎皮質ホルモン剤を投与しても免疫関連の副作用が管理できない患者には、他の全身性免疫抑制剤の投与を検討する。

以下に議論する副作用に関する毒性管理指針では、必ずしも全身性ステロイドの投与を要求していない（例、内分泌障害及び皮膚反応）。

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免疫関連の肺臓炎

KEYTRUDA は、免疫関連の肺臓炎を引き起こす可能性がある。肺臓炎の発現割合は、胸部照射歴のある患者で高い。KEYTRUDA の投与を受けた患者の3.4%（94/2799例）に免疫関連の肺臓炎が発現した。このうち、死亡に至る副作用は0.1%、Grade 4は0.3%、Grade 3は0.9%、Grade 2は1.3%であった。肺臓炎がみられた患者の67%（63/94例）は全身性副腎皮質ホルモン剤の投与を必要とした。肺臓炎による投与中止は1.3%（36例）、休薬は0.9%（26例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開したが、このうち23%で肺臓炎が再発した。肺臓炎が発現した患者94例中59%は回復した。

KEYTRUDA の単独投与を受けた古典的ホジキンリンパ腫を有する389例の成人患者が組み入れられた臨床試験では、31例（8%）に肺臓炎が発現した。このうち、Grade 3-4の肺臓炎の発現割合は2.3%であった。患者は高用量の副腎皮質ホルモン剤を投与［投与期間の中央値は10日（範囲：2日～53ヵ月）］された。肺臓炎の発現割合は、胸部照射歴の有無にかかわらず同程度であった。肺臓炎による投与中止は21例（5.4%）で認められた。肺臓炎が発現した患者のうち42%は休薬し、68%は投与を中止し、77%は回復した。

外科的切除後の非小細胞肺癌を有する580例の成人患者が組み入れられた臨床試験（KEYNOTE-091試験）では、41例（7%）に肺臓炎が発現した。このうち、死亡に至る副作用は0.2%、Grade 4は0.3%、Grade 3は1%であった。患者は高用量の副腎皮質ホルモン剤を投与［投与期間の中央値は10日（範囲：1日～2.3ヵ月）］された。肺臓炎による投与中止は26例（4.5%）で認められた。肺臓炎が発現した患者のうち54%は休薬し、63%は投与を中止し、71%は回復した。

免疫関連の大腸炎

KEYTRUDA は、下痢を呈する免疫関連の大腸炎を引き起こす可能性がある。副腎皮質ホルモン剤抵抗性の免疫関連の大腸炎をきたす患者で、サイトメガロウイルス（CMV）感染／再燃が報告されている。副腎皮質ホルモン剤抵抗性の大腸炎の場合、ほかの病因を除外するため感染症検査の再実施を検討する。KEYTRUDA の投与を受けた患者の1.7%（48/2799例）に免疫関連の大腸炎が発現した。このうち、Grade 4は0.1%未満、Grade 3は1.1%、Grade 2は0.4%であった。大腸炎がみられた患者の69%（33/48例）で、全身性副腎皮質ホルモン剤の投与を必要とした。患者の4.2%ではさらなる免疫抑制剤の投与を必要とした。大腸炎による投与中止は0.5%（15例）、休薬は0.5%（13例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開したが、このうち23%で大腸炎が再発した。大腸炎が発現した患者48例中85%は回復した。

肝毒性及び免疫関連の肝炎

KEYTRUDA 単独投与

KEYTRUDA は、免疫関連の肝炎を引き起こす可能性がある。KEYTRUDA の投与を受けた患者の0.7%（19/2799例）に免疫関連の肝炎が発現した。このうち、Grade 4は0.1%未満、Grade 3は0.4%、Grade 2は0.1%であった。肝炎がみられた患者の68%（13/19例）で、全身性副腎皮質ホルモン剤の

投与を必要とした。このうち11%ではさらなる免疫抑制剤の投与を必要とした。肝炎による投与中止は0.2%（6例）、休薬は0.3%（9例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開し、再発例はなかった。肝炎が発現した患者19例中79%は回復した。

KEYTRUDA とアキシチニブとの併用投与

KEYTRUDA とアキシチニブの併用投与により、KEYTRUDA 単独投与よりも高い頻度で、Grade 3及び4の ALT 及び AST 増加を伴う肝毒性を引き起こす可能性がある。投与開始前及び投与期間中は定期的に肝機能検査を行うこと。単独投与時よりも頻回の肝機能検査を考慮する。肝酵素が上昇した場合、KEYTRUDA 及びアキシチニブを休薬し、必要に応じて副腎皮質ホルモン剤の投与を検討すること［用法・用量（2.3）参照］。

KEYTRUDA とアキシチニブの併用投与により、Grade 3及び4の ALT 増加（20%）及び AST 増加（13%）がみられた。ALT 増加がみられた患者の59%が全身性副腎皮質ホルモン剤の投与を受けた。基準値上限の3倍以上の ALT 増加がみられた患者（Grade 2-4、116例）のうち94%は、ALT が Grade 1以下に回復した。KEYTRUDA（3例）、アキシチニブ（34例）又はその両剤（55例）が再投与された92例のうち、基準値上限の3倍以上の ALT 増加の再発がみられたのは、KEYTRUDA 投与患者1例、アキシチニブ投与患者16例、両剤投与患者24例であった。これらの患者はすべて、その後回復した。

免疫関連の内分泌障害

副腎機能不全

KEYTRUDA は、初発及び続発性の副腎機能不全を引き起こす可能性がある。Grade 2以上の副腎機能不全に対して、臨床的に必要であれば、ホルモン補充療法を含む対症療法を開始する。程度に応じて本剤を休薬すること［用法・用量（2.3）参照］。

KEYTRUDA の投与を受けた2799例中22例（0.8%）に副腎機能不全が発現した。このうち、Grade 4は0.1%未満、Grade 3は0.3%、Grade 2は0.3%であった。副腎機能不全がみられた患者の77%（17/22例）で全身性副腎皮質ホルモン剤の投与が必要とされた。このうち大半が、全身性副腎皮質ホルモン剤の投与を継続した。副腎機能不全による投与中止は0.1%未満（1例）で認められ、休薬は0.3%（8例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。

下垂体炎

KEYTRUDA は、免疫関連の下垂体炎を引き起こす可能性がある。下垂体炎は、頭痛、羞明又は視野欠損といった、mass effect に関連する急性症状を呈する。下垂体炎は下垂体機能低下症を引き起こす可能性がある。必要であれば、ホルモン補充療法を開始すること。程度に応じて本剤を休薬又は中止すること［用法・用量（2.3）参照］。

KEYTRUDA の投与を受けた患者の0.6%（17/2799例）に下垂体炎が発現した。このうち、Grade 4は0.1%未満、Grade 3は0.3%、Grade 2は0.2%であった。下垂体炎がみられた患者の94%（16/17例）

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で全身性副腎皮質ホルモン剤の投与を必要とした。このうち大半が、全身性副腎皮質ホルモン剤の投与を継続した。下垂体炎による投与中止は0.1%（4例）で認められ、休薬は0.3%（7例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。

甲状腺機能障害

KEYTRUDA は、免疫関連の甲状腺機能障害を引き起こす可能性がある。甲状腺炎は内分泌障害の有無にかかわらず発現する可能性がある。甲状腺機能亢進症に続いて甲状腺機能低下症が発現することもある。臨床的に必要であれば、甲状腺機能低下症の場合にはホルモン補充療法を開始し、甲状腺機能亢進症の場合には医療機関での管理を開始する。程度に応じて本剤を休薬又は中止すること［用法・用量（2.3）参照］。

KEYTRUDA の投与を受けた患者の0.6%（16/2799例）に甲状腺炎が発現した。このうち、Grade 2は0.3%であった。甲状腺炎による投与中止例はなかった。甲状腺炎による休薬は0.1%未満（1例）で認められた。

KEYTRUDA の投与を受けた患者の3.4%（96/2799例）に甲状腺機能亢進症が発現した。このうち、Grade 3は0.1%、Grade 2は0.8%であった。甲状腺機能亢進症による投与中止は0.1%未満（2例）で認められ、休薬は0.3%（7例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。

甲状腺機能亢進症の新たな発現又は増悪の割合は、外科的切除後に KEYTRUDA の単独投与による術後補助療法を受けた非小細胞肺癌患者580例の中で高く（11%）（KEYNOTE-091試験）、その中には Grade 3の甲状腺機能亢進症（0.2%）が含まれていた。

KEYTRUDA の投与を受けた患者の8%（237/2799例）で甲状腺機能低下症が発現した。このうち、Grade 3は0.1%、Grade 2は6.2%であった。甲状腺機能低下症による投与中止は0.1%未満（1例）で認められ、休薬は0.5%（14例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。甲状腺機能低下症が発現した患者の大半は、長期間の甲状腺ホルモン補充療法を必要とした。

甲状腺機能低下症の新たな発現又は増悪の割合は、KEYTRUDA の単独投与又はプラチナ製剤及びフルオロウラシルとの併用投与を受けた頭頸部扁平上皮癌患者1185例の中で高く（16%）、その中には Grade 3の甲状腺機能低下症（0.3%）が含まれていた。甲状腺機能低下症の新たな発現又は増悪の割合は、KEYTRUDA の単独投与を受けた古典的ホジキンリンパ腫患者389例の中で高く（17%）、その中には Grade 1（6.2%）及び Grade 2（10.8%）の甲状腺機能低下症が含まれていた。

甲状腺機能低下症の新たな発現又は増悪の割合は、外科的切除後に KEYTRUDA の単独投与による術後補助療法を受けた非小細胞肺癌患者580例の中で高く（22%）（KEYNOTE-091試験）、その中には Grade 3の甲状腺機能低下症（0.3%）が含まれていた。

1型糖尿病、糖尿病性ケトアシドーシスを含む

高血糖又は糖尿病のその他の徴候及び症状をモニタリングすること。臨床的に必要であれば、インスリン投与を開始すること。程度に応じて本剤を休薬すること［用法・用量（2.3）参照］。

KEYTRUDA の投与を受けた患者の0.2%（6/2799例）で1型糖尿病が発現した。1型糖尿病による投与中止は0.1%未満（1例）であり、休薬も0.1%未満（1例）であった。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。1型糖尿病が発現した患者はすべて、長期間のインスリン投与を必要とした。

免疫関連の腎炎及び腎機能障害

KEYTRUDA は、免疫関連の腎炎を引き起こす可能性がある。KEYTRUDA の投与を受けた患者の0.3%（9/2799例）で免疫関連の腎炎が発現した。このうち、Grade 4は0.1%未満、Grade 3は0.1%、Grade 2は0.1%であった。腎炎が発現した患者の89%（8/9例）が全身性副腎皮質ホルモン剤の投与を必要とした。腎炎による投与中止は0.1%（3例）で認められ、休薬も0.1%（3例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。このうち、腎炎が再発した患者はいなかった。腎炎が発現した患者9例のうち56%は回復した。

免疫関連の皮膚の副作用

KEYTRUDA は、免疫関連の発疹又は皮膚炎を引き起こす可能性がある。PD-1/PD-L1抗体を投与すると、スティーヴンス・ジョンソン症候群、DRESS 及び中毒性表皮壊死融解症（TEN）などの剥脱性皮膚炎が発現した。軽度から中等度の非剥脱性発疹の治療には皮膚軟化剤及び／又は局所性副腎皮質ホルモン剤の投与が適している。程度に応じて本剤を休薬又は中止すること［用法・用量（2.3）参照］。

KEYTRUDA の投与を受けた患者の1.4%（38/2799例）で免疫関連の皮膚の副作用が発現した。このうち、Grade 3は1%、Grade 2は0.1%であった。免疫関連の皮膚の副作用が発現した患者の40%（15/38例）は全身性副腎皮質ホルモン剤の投与を必要とした。

免疫関連の皮膚の副作用による投与中止は0.1%（2例）で認められ、休薬は0.6%（16例）で認められた。KEYTRUDA を休薬したすべての患者で症状改善後に投与を再開した。このうち、6%では免疫関連の皮膚の副作用が再発した。免疫関連の皮膚の副作用が発現した患者38例のうち79%は回復した。

その他の免疫関連の副作用

KEYTRUDA の投与を受けた患者又はその他の PD-1/PD-L1抗体の投与後に報告された、発現割合が1%未満（特に記載のない限り）の臨床的に重要な免疫関連の副作用を以下に記載する。これらの一部は重度又は死亡に至ると報告されている。

- *心臓／血管系*：心筋炎、心膜炎、血管炎
- *神経系*：髄膜炎、脳炎、脊髄炎及び脱髄、筋無力症候群／重症筋無力症（増悪を含む）、ギラン・バレー症候群、神経不全麻痺、自己免疫性ニューロパチー

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- *眼*：ぶどう膜炎、虹彩炎及び眼のその他の炎症性毒性が発現する可能性がある。網膜剥離を伴う症例もある。失明を含むさまざまな程度の視力障害が発現する可能性がある。ぶどう膜炎がその他の免疫関連の副作用とともに発現した場合、フォークト・小柳・原田症候群を考慮する。この場合、恒久的な失明のリスクを低下させるため、全身性ステロイドの投与が必要となる。
- *胃腸管系*：膵炎（アミラーゼ及びリパーゼの血清中濃度増加を含む）、胃炎、十二指腸炎
- 筋骨格系及び結合組織：筋炎／多発性筋炎、横紋筋融解症（及び腎不全を含むその後遺症）、関節炎（1.5%）、リウマチ性多発筋痛
- *内分泌系*：副甲状腺機能低下症
- *血液／免疫系*：溶血性貧血、再生不良性貧血、血球貪食性リンパ組織球症、全身性炎症反応症候群、組織球性壊死性リンパ節炎（菊池病）、サルコイドーシス、免疫性血小板減少性紫斑病、実質臓器移植拒絶反応、その他の移植（角膜移植を含む）拒絶反応

5.2　Infusion-related reaction

KEYTRUDA は、重度及び生命を脅かす Infusion-related reaction（過敏症及びアナフィラキシーを含む）を引き起こす可能性があり、投与を受けた2799例の0.2%に発現した。悪寒（rigors）、悪寒（chills）、喘鳴、そう痒症、潮紅、発疹、低血圧、低酸素血症及び発熱を含む Infusion-related reaction の徴候及び症状をモニタリングすること。軽度（Grade 1）又は中等度（Grade 2）の Infusion-related reaction が発現した場合は注入を中断又は注入速度を下げる。重度（Grade 3）又は生命を脅かす（Grade 4）Infusion-related reaction が発現した場合は注入を中止し、本剤を中止すること［用法・用量（2.3）参照］。

5.3　同種造血幹細胞移植に伴う合併症

同種造血幹細胞移植（HSCT）を受ける患者において、PD-1/PD-L1抗体の投与前又は投与後に、死亡に至る及びその他の重篤な合併症が発現する可能性がある。移植関連の合併症として、超急性移植片対宿主病（GVHD）、急性 GVHD、慢性 GVHD、強度減弱前処置後の肝中心静脈閉塞症（VOD）及びステロイド投与を要する発熱性症候群（感染原因は特定されない）がある。これらの合併症は、PD-1/PD-L1抗体の投与と同種造血幹細胞移植の間に介入治療した場合でも発現する可能性がある。

移植関連の合併症について、患者を注意深く観察し、迅速な治療介入を行うこと。同種造血幹細胞移植の前又は後に PD-1/PD-L1抗体を投与する場合は、ベネフィットとリスクを考慮すること。

5.4　多発性骨髄腫患者に対してサリドマイドアナログ及びデキサメタゾンに KEYTRUDA を追加投与した際の死亡の増加

多発性骨髄腫（PD-1又は PD-L1阻害剤が不適応）の患者を対象とした2つの無作為化試験において、サリドマイドアナログ及びデキサメタゾンに KEYTRUDA を追加投与した際に、死亡の増加

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が認められた。管理された臨床試験以外で、多発性骨髄腫の患者にサリドマイドアナログ及びデキサメタゾンと PD-1又は PD-L1阻害剤を併用投与することは推奨されない。

5.5　胚・胎児毒性

KEYTRUDA の作用機序から、妊婦に投与した場合、胎児に危険を及ぼす可能性がある。動物モデルでは、胎児組織に対する母体の免疫寛容を、PD-1/PD-L1シグナル伝達経路が誘導することにより妊娠を維持することが示されている。本剤の胎児への潜在的なリスクを女性患者に伝えること。妊娠する可能性のある女性には、本剤の投与中及び投与終了後4ヵ月間は有効な避妊方法を用いることを助言すること［特殊集団への投与（8.1、8.3）参照］。

有害事象

6　副作用

以下の臨床的に重要な副作用については、別のセクションで詳細に記載する。

- 重度及び死亡に至る免疫関連の副作用［警告及び使用上の注意（5.1）参照］
- Infusion-related reaction［警告及び使用上の注意（5.2）参照］

6.1　臨床試験での経験

臨床試験は様々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有害事象の発現割合は、別の薬剤の臨床試験での発現割合と直接比較することができない。また、臨床現場で認められる発現割合を反映しない可能性がある。

「警告及び使用上の注意」の記載は、KEYTRUDA の単独投与を受けた患者2799例の結果を反映したものであり、悪性黒色腫患者912例及び非小細胞肺癌患者682例を組み入れた3つの無作為化、非盲検、実薬対照の臨床試験（KEYNOTE-002、006及び010試験）、悪性黒色腫患者655例及び非小細胞肺癌患者550例を組み入れた単群試験（KEYNOTE-001試験）が含まれる。2799例の患者に加え、「警告及び使用上の注意」の特定の小項目では、以下の臨床試験で観察された有害事象を記載している：KEYTRUDA を単独投与した試験として、外科的切除後の非小細胞肺癌患者580例を組み入れた無作為化、プラセボ対照試験（KEYNOTE-091試験）、頭頸部扁平上皮癌患者909例を組み入れた、非無作為化、非盲検、マルチコホート試験（KEYNOTE-012試験）、非無作為化、非盲検、単群試験（KEYNOTE-055試験）及び2つの無作為化、非盲検、実薬対照試験（KEYNOTE-040及び048試験の単独投与群）；古典的ホジキンリンパ腫患者389例を組み入れた2つの非無作為化、非盲検試験（KEYNOTE-013及び087試験）及び無作為化、非盲検、実薬対照試験（KEYNOTE-204試験）；頭頸部扁平上皮癌患者276例を組み入れた無作為化、非盲検、実薬対照試験（KEYNOTE-048試験の併用投与群）；腎細胞癌患者429例を組み入れアキシチニブと併用投与した無作為化、実薬対照試験（KEYNOTE-426試験）；並びに市販後の使用経験。これらの臨床試験を通して、KEYTRUDA 2 mg/kg を3週間間隔、10 mg/kg を2週間間隔、10 mg/kg を3週間間隔又は200 mg を3週間間隔で静脈内投与した。2799例のうち、6ヵ月以上 KEYTRUDA の投与を受けた患者は41%、12ヵ月以上投

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与を受けた患者は21%であった。

悪性黒色腫

イピリムマブ未治療の悪性黒色腫

KEYNOTE-006試験では、イピリムマブ未治療で前治療として1レジメンの全身療法を受けた切除不能又は転移性の悪性黒色腫患者に KEYTRUDA を投与した際の安全性を評価した。KEYNOTE-006試験は多施設、非盲検、実薬対照の臨床試験であり、患者は無作為割付け（1：1：1）され、疾患進行又は許容できない副作用が発現するまで KEYTRUDA を10 mg/kg 2週間間隔（278例）又は10 mg/kg 3週間間隔（277例）、又は疾患進行又は許容できない副作用が発現した場合の早期中止を除きイピリムマブを3 mg/kg 3週間間隔で4回まで投与（256例）した［臨床試験（14.1）参照］。また、自己免疫疾患、全身性の副腎皮質ホルモン剤及び他の免疫抑制剤による治療を要する疾患（間質性肺疾患の既往）、HIV 又は B 型若しくは C 型肝炎を含む治療を要する活動性の感染を有する患者は不適格とされた。

KEYTRUDA の投与期間の中央値は5.6ヵ月（範囲：1日～11.0ヵ月）であり、KEYTRUDA 両群で同様であった。6ヵ月以上 KEYTRUDA の投与を受けた患者の割合は KEYTRUDA 10 mg/kg 2週間間隔投与及び10 mg/kg 3週間間隔投与でそれぞれ51%及び46%であり、両群で1年を超えて投与を受けた患者はいなかった。

試験集団の背景因子は、年齢の中央値が62歳（範囲：18～89歳）であり、男性の割合は60%、白人が98%、LDH 上昇が32%、M1c が65%、脳転移の既往が9%、全身療法を受けた患者は約36%であり、BRAF 阻害剤が15%、化学療法が13%、免疫療法が6%であった。

KEYNOTE-006試験の安全性プロファイルは2週間間隔投与及び3週間間隔投与で同様であった。したがって、安全性の概要として、KEYTRUDA の両群を併合（555例）した解析結果を示す。9%の患者が有害事象により KEYTRUDA の投与を中止した。2例以上の患者で投与中止に至った有害事象は、大腸炎（1.4%）、自己免疫性肝炎（0.7%）、アレルギー反応（0.4%）、多発ニューロパチー（0.4%）及び心不全（0.4%）であった。21%の患者が有害事象により KEYTRUDA を休薬し、高頻度に認められた（1%以上）KEYTRUDA の休薬に至った有害事象は、下痢（2.5%）であった。[表 1.6.2-4]及び[表 1.6.2-5]に、KEYNOTE-006試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-4　　有害事象†
KEYTRUDA の投与を受けた切除不能又は転移性の悪性黒色腫患者で発現割合 10%以上
（KEYNOTE-006 試験）

有害事象	KEYTRUDA 10 mg/kg 2週間間隔及び3週間間隔投与 (555例)		イピリムマブ投与 (256例)	
	All Grades‡ (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)

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一般・全身障害および投与部位の状態				
疲労	28	0.9	28	3.1
皮膚および皮下組織障害				
発疹§	24	0.2	23	1.2
尋常性白斑‖	13	0	2	0
筋骨格系および結合組織障害				
関節痛	18	0.4	10	1.2
背部痛	12	0.9	7	0.8
呼吸器、胸郭および縦隔障害				
咳嗽	17	0	7	0.4
呼吸困難	11	0.9	7	0.8
代謝および栄養障害				
食欲減退	16	0.5	14	0.8
神経系障害				
頭痛	14	0.2	14	0.8

† イピリムマブ群と同程度又はそれ以上の発現割合であった有害事象を選択した。
‡ Grade 分類は NCI CTCAE v4.0に基づく。
§ 発疹、紅斑性皮疹、毛孔性皮疹、全身性発疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹及び剥脱性発疹を含む。
‖ 皮膚色素減少を含む。

KEYTRUDA を投与された患者で10%以上に認められたその他の臨床的に重要な有害事象は、下痢（26%）及び悪心（21%）及びそう痒症（17%）であった。

表 1.6.2-5　　ベースラインから悪化した臨床検査値異常†
KEYTRUDA の投与を受けた切除不能又は転移性の悪性黒色腫患者で発現割合 20%以上
（KEYNOTE-006 試験）

臨床検査‡	KEYTRUDA 10 mg/kg 2週間間隔及び3週間間隔投与		イピリムマブ投与	
	All Grades§ (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
血清生化学				
高血糖	45	4.2	45	3.8
高トリグリセリド血症	43	2.6	31	1.1
低ナトリウム血症	28	4.6	26	7
AST 増加	27	2.6	25	2.5
高コレステロール血症	20	1.2	13	0
血液				
貧血	35	3.8	33	4.0
リンパ球減少症	33	7	25	6

† イピリムマブ群と同程度又はそれ以上の発現割合であった臨床検査値異常を選択した。
‡ 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA 群：520～546例、イピリムマブ群：237～247例であり、高トリグリセリド血症については、KEYTRUDA 群：429例、イピリムマブ群：183例、高コレステロール血症については、KEYTRUDA 群：484例、イピリムマブ群：205例。
§ Grade 分類は NCI CTCAE v4.0に基づく。

KEYTRUDA を投与された患者で20%以上に認められたその他の臨床的に重要な臨床検査値異常は、低アルブミン血症（All Grades：27%、Grade 3-4：2.4%）、ALT 増加（All Grades：23%、Grade 3-4：3.1%）、及びアルカリホスファターゼ増加（All Grades：21%、Grade 3-4：2%）であった。

<u>イピリムマブ抵抗性の悪性黒色腫</u>

KEYNOTE-002試験では、イピリムマブ治療後及び BRAF V600変異陽性の場合は BRAF 阻害剤

治療後に疾患進行した切除不能又は転移性の悪性黒色腫患者に KEYTRUDA を投与した際の安全性を評価した。KEYNOTE-002試験は多施設、一部盲検（KEYTRUDA の用量）、無作為化（1：1：1）、実薬対照の臨床試験であり、患者（528例）は KEYTRUDA を2 mg/kg（178例）又は10 mg/kg（179例）で3週間間隔、又は治験担当医師が選択した化学療法（171例）が投与された。化学療法の選択肢は、ダカルバジン（26%）、テモゾロミド（25%）、パクリタキセル／カルボプラチンの併用（25%）、パクリタキセル（16%）、カルボプラチン（8%）であった［臨床試験（14.1）参照］。また、自己免疫疾患、イピリムマブによる重度の免疫関連の副作用［Grade 4又は12週を超えて副腎皮質ホルモン剤（プレドニゾロン換算10 mg／日以上）による治療を要する Grade 3の副作用）］、全身性の副腎皮質ホルモン剤及び他の免疫抑制剤による治療を要する疾患、間質性肺疾患の既往、HIV 又は B 型若しくは C 型肝炎を含む治療を要する活動性の感染を有する患者は不適格とされた。

KEYTRUDA 2 mg/kg 3週間間隔投与の投与期間の中央値は3.7ヵ月（範囲：1日～16.6ヵ月）であり、KEYTRUDA 10 mg/kg 3週間間隔投与の投与期間の中央値は4.8ヵ月（範囲：1日～16.8ヵ月）であった。KEYTRUDA 2 mg/kg 投与で6ヵ月以上 KEYTRUDA の投与を受けた患者の割合は36%、12ヵ月以上投与を受けた患者の割合は4%であり、KEYTRUDA 10 mg/kg 投与で6ヵ月以上 KEYTRUDA の投与を受けた患者の割合は41%、12ヵ月以上投与を受けた患者の割合は6%であった。

試験集団の背景因子は、年齢の中央値が62歳（範囲：15～89歳）であり、男性の割合は61%、白人が98%、LDH 上昇が41%、M1c が83%、進行性及び転移性の悪性黒色腫に対する前治療を2レジメン以上受けた患者は73%（イピリムマブが100%、BRAF 阻害剤が25%）であり、脳転移の既往が15%であった。

KEYNOTE-002試験の安全性プロファイルは2 mg/kg 投与及び10 mg/kg 投与で同様であった。したがって、安全性の概要として、KEYTRUDA の両群を併合（357例）した解析結果を示す。12%の患者が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた（1%以上）投与中止に至った有害事象は、全身健康状態低下（1%）、無力症（1%）、呼吸困難（1%）、肺臓炎（1%）及び全身性浮腫（1%）であった。14%の患者が有害事象により KEYTRUDA を休薬し、高頻度に認められた（1%以上）KEYTRUDA の休薬に至った有害事象は、呼吸困難（1%）、下痢（1%）及び斑状丘疹状皮疹（1%）であった。[表　1.6.2-6]及び[表　1.6.2-7]に、KEYNOTE-002試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-6　　有害事象†

KEYTRUDA の投与を受けた悪性黒色腫患者で発現割合 10%以上（KEYNOTE-002 試験）

有害事象	KEYTRUDA 2 mg/kg 及び10 mg/kg 3週間間隔投与(357例)		化学療法‡ (171例)	
	All Grades§ (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)

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皮膚および皮下組織障害				
そう痒症	28	0	8	0
発疹‖	24	0.6	8	0
胃腸障害				
便秘	22	0.3	20	2.3
下痢	20	0.8	20	2.3
腹痛	13	1.7	8	1.2
呼吸器、胸郭および縦隔障害				
咳嗽	18	0	16	0
一般・全身障害および投与部位の状態				
発熱	14	0.3	9	0.6
無力症	10	2.0	9	1.8
筋骨格系および結合組織障害				
関節痛	14	0.6	10	1.2

† 化学療法群と同程度又はそれ以上の発現割合であった有害事象を選択した。
‡ 化学療法：ダカルバジン、テモゾロミド、カルボプラチン／パクリタキセルの併用、パクリタキセル、又はカルボプラチン
§ Grade 分類は NCI CTCAE v4.0に基づく。
‖ 発疹、紅斑性皮疹、全身性発疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹及びそう痒性皮疹を含む。

KEYTRUDA を投与された患者で認められたその他の臨床的に重要な有害事象は、疲労（43%）、悪心（22%）、食欲減退（20%）、嘔吐（13%）及び末梢性ニューロパチー（1.7%）であった。

表 1.6.2-7　　ベースラインから悪化した臨床検査値異常†
KEYTRUDA の投与を受けた悪性黒色腫患者で発現割合 20%以上（KEYNOTE-002 試験）

臨床検査‡	KEYTRUDA 2 mg/kg 及び10 mg/kg 3週間間隔投与		化学療法	
	All Grades§ (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
血清生化学				
高血糖	49	6	44	6
低アルブミン血症	37	1.9	33	0.6
低ナトリウム血症	37	7	24	3.8
高トリグリセリド血症	33	0	32	0.9
アルカリホスファターゼ増加	26	3.1	18	1.9
AST 増加	24	2.2	16	0.6
血中重炭酸塩減少	22	0.4	13	0
低カルシウム血症	21	0.3	18	1.9
ALT 増加	21	1.8	16	0.6

† 化学療法群と同程度又はそれ以上の発現割合であった臨床検査値異常を選択した。
‡ 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA 群：320～325例、化学療法群：154～161例であり、高トリグリセリド血症については、KEYTRUDA 群：247例、化学療法群：116例、血中重炭酸塩減少については、KEYTRUDA 群：263例、化学療法群：123例。
§ Grade 分類は NCI CTCAE v4.0に基づく。

KEYTRUDA を投与された患者で20%以上に認められたその他の臨床検査値異常は、貧血（All Grades：44%、Grade 3-4：10%）及びリンパ球減少症（All Grades：40%、Grade 3-4：9%）であった。

ⅡB 期又はⅡC 期の悪性黒色腫切除後の術後補助療法

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KEYNOTE-716試験は、ⅡB 期又はⅡC 期の悪性黒色腫患者969例［臨床試験（14.1）参照］にKEYTRUDA を投与し、KEYTRUDA の投与期間の中央値は9.9ヵ月（範囲：0～15.4ヵ月）であった。自己免疫疾患を有する患者、免疫抑制剤による治療を要する医学的状態の患者、粘膜又は眼の悪性黒色腫を有する患者は不適格とされた。ⅡB 期又はⅡC 期の悪性黒色腫患者に認められた有害事象は、KEYNOTE-054試験に組み入れられたⅢ期の悪性黒色腫患者1011例又は KEYTRUDA を単独投与された悪性黒色腫又は NSCLC 患者2799例に認められた有害事象と同様であった。

Ⅲ期の悪性黒色腫切除後の術後補助療法

KEYNOTE-054試験は、ⅢA 期（リンパ節転移1 mm 超）、ⅢB 期又はⅢC 期の悪性黒色腫に対して完全切除を行った患者1019例に、KEYTRUDA 200 mg を3週間間隔で点滴静注（509例）又はプラセボ（502例）を最長1年間投与した無作為化（1：1）二重盲検試験［臨床試験（14.1）参照］であり、KEYTRUDA の単独投与時の安全性を評価した。活動性の自己免疫疾患を有する患者、免疫抑制剤による治療を要する医学的状態の患者、粘膜又は眼の悪性黒色腫を有する患者は不適格とされた。76%の患者が6ヵ月以上 KEYTRUDA を投与された。

試験集団の背景因子は、年齢の中央値が54歳（範囲：19～88歳）、65歳以上が25%、男性の割合が62%、ECOG PS が0の患者が94%及び ECOG PS が1の患者が6%であった。IIIA 期が16%、IIIB 期が46%、IIIC 期（1～3個のリンパ節転移）が18%、IIIC 期（4個以上のリンパ節転移）が20%であった。

KEYTRUDA の投与を受けた患者の2例が疾患進行以外の原因により死亡した。死因は好酸球増加と全身症状を伴う薬物反応、及び呼吸不全を伴う自己免疫性筋炎であった。KEYTRUDA の投与を受けた患者の25%が重篤な有害事象を発現した。KEYTRUDA の投与を受けた患者の14%が有害事象により投与を中止した。高頻度（1%以上）に認められた投与中止に至った有害事象は肺臓炎（1.4%）、大腸炎（1.2%）及び下痢（1%）であった。KEYTRUDA の投与を受けた患者の19%が有害事象により投与を休薬し、高頻度（1%以上）に認められた休薬に至った有害事象は下痢（2.4%）、肺臓炎（2%）、ALT 増加（1.4%）、関節痛（1.4%）、AST 増加（1.4%）、呼吸困難（1%）及び疲労（1%）であった。[表 1.6.2-8]及び[表 1.6.2-9]に、KEYNOTE-054試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-8　　有害事象†

KEYTRUDA の投与を受けた悪性黒色腫患者で発現割合 10%以上（KEYNOTE-054 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（509例）		プラセボ（502例）	
	All Grades‡ (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
胃腸障害				
下痢	28	1.2	26	1.2
悪心	17	0.2	15	0
皮膚および皮下組織障害				
そう痒症	19	0	12	0
発疹	13	0.2	9	0
筋骨格系および結合組織障害				

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関節痛	16	1.2	14	0
内分泌障害				
甲状腺機能低下症	15	0	2.8	0
甲状腺機能亢進症	10	0.2	1.2	0
呼吸器、胸郭および縦隔障害				
咳嗽	14	0	11	0
一般・全身障害および投与部位の状態				
無力症	11	0.2	8	0
インフルエンザ様疾患	11	0	8	0
臨床検査				
体重減少	11	0	8	0

† プラセボ群と同程度又はそれ以上の発現割合であった有害事象を選択した。
‡ Grade 分類は NCI CTCAE v4.03に基づく。

表 1.6.2-9　ベースラインから悪化した臨床検査値異常†
KEYTRUDA の投与を受けた悪性黒色腫患者で発現割合 20%以上（KEYNOTE-054 試験）

臨床検査‡	KEYTRUDA 200 mg 3週間間隔投与		プラセボ	
	All Grades§ (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
血清生化学				
ALT 増加	27	2.4	16	0.2
AST 増加	24	1.8	15	0.4
血液				
リンパ球減少症	24	1	16	1.2

† プラセボ群と同程度又はそれ以上の発現割合であった臨床検査値異常を選択した。
‡ 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA 群：503～507例、プラセボ群：492～498例。
§ Grade 分類は NCI CTCAE v4.03に基づく。

非小細胞肺癌

未治療で転移性の非扁平上皮非小細胞肺癌（ペメトレキセド及びプラチナ製剤化学療法との併用）

KEYNOTE-189試験は、多施設共同、二重盲検、無作為化（2：1）、実薬対照の臨床試験であり、EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性ではない、未治療で転移性の非扁平上皮非小細胞肺癌患者を対象に、KEYTRUDA とペメトレキセド及び治験担当医師が選択したプラチナ製剤化学療法（カルボプラチン又はシスプラチン）を投与した際の安全性を評価した［臨床試験（14.2）参照］。計607例が、KEYTRUDA 200 mg とペメトレキセド及びプラチナ製剤を3週間間隔で4コース併用投与後に KEYTRUDA とペメトレキセドとの併用投与（405例）又はプラセボとペメトレキセド及びプラチナ製剤を3週間間隔で4コース併用投与後にプラセボとペメトレキセドとの併用投与（202例）を受けた。治験薬初回投与前2年以内に全身療法を必要とした自己免疫疾患を有する患者、免疫抑制剤治療を必要とした患者、又は治験薬初回投与前26週間以内に30 Gy を超える胸部に対する放射線療法を受けていた患者は不適格とされた。

KEYTRUDA 200 mg 3週間間隔投与の投与期間の中央値は、7.2ヵ月（範囲：1日～20.1ヵ月）であった。6ヵ月以上 KEYTRUDA の投与を受けた患者の割合は60%であった。カルボプラチンの投

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与を受けた患者の割合は72%であった。

試験集団の背景因子は、年齢の中央値が64歳（範囲：34～84歳）、65歳以上が49%、男性の割合が59%、白人が94%、アジア人が3%、ベースライン時に脳転移の既往を有していた患者が18%であった。

KEYTRUDA の投与を受けた患者の20%が有害事象により投与を中止した。高頻度に認められた投与中止に至った有害事象は、肺臓炎（3%）及び急性腎障害（2%）であった。KEYTRUDA の投与を受けた患者の53%が有害事象により投与を休薬し、高頻度（2%以上）に認められた休薬に至った有害事象又は臨床検査値異常は、好中球減少症（13%）、無力症／疲労（7%）、貧血（7%）、血小板減少症（5%）、下痢（4%）、肺炎（4%）、血中クレアチニン増加（3%）、呼吸困難（2%）、発熱性好中球減少症（2%）、上気道感染（2%）、ALT 増加（2%）及び発熱（2%）であった。[表 1.6.2-10]及び[表 1.6.2-11]に、KEYNOTE-189試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-10　　有害事象
KEYTRUDA の投与を受けた非扁平上皮非小細胞肺癌患者で発現割合 20%以上
（KEYNOTE-189 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与とペメトレキセド及びプラチナ製剤化学療法との併用（405例）		プラセボとペメトレキセド及びプラチナ製剤化学療法との併用（202例）	
	All Grades* (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
胃腸障害				
悪心	56	3.5	52	3.5
便秘	35	1.0	32	0.5
下痢	31	5	21	3.0
嘔吐	24	3.7	23	3.0
一般・全身障害および投与部位の状態				
疲労†	56	12	58	6
発熱	20	0.2	15	0
代謝および栄養障害				
食欲減退	28	1.5	30	0.5
皮膚および皮下組織障害				
発疹‡	25	2.0	17	2.5
呼吸器、胸郭および縦隔障害				
咳嗽	21	0	28	0
呼吸困難	21	3.7	26	5

* Grade 分類は NCI CTCAE v4.03に基づく。
† 無力症及び疲労を含む。
‡ 性器発疹、発疹、全身性皮疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹及び膿疱性皮疹を含む。

表 1.6.2-11　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた非扁平上皮非小細胞肺癌患者で発現割合 20%以上
（KEYNOTE-189 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与とペ	プラセボとペメトレキセド及びプラチ

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	メトレキセド及びプラチナ製剤化学療法との併用		ナ製剤化学療法との併用	
	All Grades† (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
血液				
貧血	85	17	81	18
リンパ球減少症	64	22	64	25
好中球減少症	48	20	41	19
血小板減少症	30	12	29	8
血清生化学				
高血糖	63	9	60	7
ALT 増加	47	3.8	42	2.6
AST 増加	47	2.8	40	1.0
低アルブミン血症	39	2.8	39	1.1
クレアチニン増加	37	4.2	25	1.0
低ナトリウム血症	32	7	23	6
低リン酸血症	30	10	28	14
アルカリホスファターゼ増加	26	1.8	29	2.1
低カルシウム血症	24	2.8	17	0.5
高カリウム血症	24	2.8	19	3.1
低カリウム血症	21	5	20	5

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA とペメトレキセド及びプラチナ製剤化学療法との併用群：381～401例、プラセボとペメトレキセド及びプラチナ製剤化学療法との併用群：184例～197例。
† Grade 分類は NCI CTCAE v4.03に基づく。

未治療で転移性の扁平上皮非小細胞肺癌（カルボプラチン及びパクリタキセル又は nab-パクリタキセル化学療法との併用）

KEYNOTE-407試験は、多施設共同、二重盲検、無作為化（1：1）、プラセボ対照の臨床試験であり、未治療で転移性の扁平上皮非小細胞肺癌患者（558例）を対象に、KEYTRUDA とカルボプラチン及び治験担当医師が選択した化学療法（パクリタキセル又は nab-パクリタキセル）を併用投与した際の安全性を評価した［臨床試験（14.2）参照］。最初の203例（KEYTRUDA と化学療法の併用投与：101例、プラセボと化学療法の併用投与：102例）の安全性データが利用可能である。治験薬初回投与前2年以内に全身療法を必要とした自己免疫疾患を有する患者、免疫抑制剤治療を必要とした患者、又は治験薬初回投与前26週間以内に30 Gy を超える胸部に対する放射線療法を受けていた患者は不適格とされた。

KEYTRUDA の投与期間の中央値は、7ヵ月（範囲：1日～12ヵ月）であった。6ヵ月以上 KEYTRUDA の投与を受けた患者の割合は61%であった。計203例のうち、カルボプラチンとパクリタキセルの投与を受けた患者が139例（68%）及びカルボプラチンと nab-パクリタキセルの投与を受けた患者が64例（32%）であった。

試験集団の背景因子は、年齢の中央値が65歳（範囲：40～83歳）、65歳以上が52%、男性の割合が78%、白人が83%、脳転移の既往を有していた患者が9%であった。

KEYTRUDA の投与を受けた患者の15%が有害事象により投与を中止したが、大多数に発現した有害事象はなかった。43%の患者が有害事象により KEYTRUDA を休薬し、発現割合が高い（2%

以上）有害事象は、血小板減少症（20%）、好中球減少症（11%）、貧血（6%）、無力症（2%）、及び下痢（2%）であった。高頻度（2%以上）に認められた重篤な有害事象は、発熱性好中球減少症（6%）、肺炎（6%）及び尿路感染（3%）であった。

KEYNOTE-407試験において KEYTRUDA と化学療法の併用投与ではプラセボと化学療法の併用投与と比較して脱毛症（47%vs36%）及び末梢性ニューロパチー（31%vs25%）の発現割合が高かったことを除いては、全般に KEYNOTE-407試験で認められた有害事象は KEYNOTE-189試験の有害事象と同様であった。

未治療の非小細胞肺癌

KEYNOTE-042試験は、多施設共同、非盲検、無作為化（1：1）、実薬対照試験であり、外科的切除若しくは根治的化学放射線療法の対象とならない未治療の PD-L1発現陽性のⅢ期の非小細胞肺癌患者、又は転移性の非小細胞肺癌患者1251人を対象に、KEYTRUDA の安全性を評価した［臨床試験（14.2）参照］。患者は KEYTRUDA 200 mg を3週間間隔（636例）、又は治験担当医師が選択した化学療法（615例）のいずれかの投与を受けた。化学療法は、ペメトレキセドとカルボプラチンの投与後、任意でペメトレキセドを3週間間隔（312例）、又はパクリタキセルとカルボプラチンの投与後、任意でペメトレキセドを3週間間隔（303例）で投与した。EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性の腫瘍を有する患者、2年以内に全身療法を必要とした自己免疫疾患を有する患者、免疫抑制剤治療を必要とした医学的状態の患者、又は26週間以内に30 Gy を超える胸部に対する放射線療法を受けた患者は不適格とされた。

KEYTRUDA の投与期間の中央値は、5.6ヵ月（範囲：1日～27.3ヵ月）であった。6ヵ月以上 KEYTRUDA 200 mg の投与を受けた患者の割合は、48%であった。

試験集団の背景因子は、年齢の中央値が63歳（範囲：25～90歳）、65歳以上が45%、男性の割合が71%、白人が64%、アジア人が30%、黒人が2%であった。19%はヒスパニック系又はラテン系であった。87%が転移性疾患（Ⅳ期）、13%がⅢ期（ⅢA 期2%、ⅢB 期11%）、ベースライン時に既治療の脳転移を有していた患者が5%であった。

KEYTRUDA の投与を受けた患者の19%が有害事象により投与を中止した。KEYTRUDA の投与中止に至った主な有害事象は肺臓炎（3.0%）、原因不明の死亡（1.6%）及び肺炎（1.4%）であった。33%の患者が有害事象により KEYTRUDA を休薬し、発現割合が高い（2%以上）有害事象又は臨床検査値異常は、肺臓炎（3.1%）、肺炎（3.0%）、甲状腺機能低下症（2.2%）及び ALT 増加（2.0%）であった。高頻度（2%以上）に認められた重篤な有害事象は、肺炎（7%）、肺臓炎（3.9%）、肺塞栓症（2.4%）及び胸水（2.2%）であった。

[表 1.6.2-12]及び[表 1.6.2-13]に、KEYNOTE-042試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-12　有害事象

KEYTRUDA の投与を受けた非小細胞肺癌患者で発現割合 10%以上（KEYNOTE-042 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（636例）		化学療法（615例）	
	All Grades* (%)	Grade 3-5 (%)	All Grades (%)	Grade 3-5 (%)
一般・全身障害および投与部位の状態				
疲労†	25	3.1	33	3.9
発熱	10	0.3	8	0
代謝および栄養障害				
食欲減退	17	1.7	21	1.5
呼吸器、胸郭および縦隔障害				
呼吸困難	17	2.0	11	0.8
咳嗽	16	0.2	11	0.3
皮膚および皮下組織障害				
発疹‡	15	1.3	8	0.2
胃腸障害				
便秘	12	0	21	0.2
下痢	12	0.8	12	0.5
悪心	12	0.5	32	1.1
内分泌障害				
甲状腺機能低下症	12	0.2	1.5	0
感染症および寄生虫症				
肺炎	12	7	9	6
臨床検査				
体重減少	10	0.9	7	0.2

* Grade 分類は NCI CTCAE v4.03に基づく。
† 疲労及び無力症を含む。
‡ 発疹、全身性皮疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹及び膿疱性皮疹を含む。

表 1.6.2-13　ベースラインから悪化した臨床検査値異常

KEYTRUDA の投与を受けた非小細胞肺癌患者で発現割合 20%以上（KEYNOTE-042 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与		化学療法	
	All Grades† (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
血清生化学				
高血糖	52	4.7	51	5
ALT 増加	33	4.8	34	2.9
低アルブミン血症	33	2.2	29	1.0
AST 増加	31	3.6	32	1.7
低ナトリウム血症	31	9	32	8
アルカリホスファターゼ増加	29	2.3	29	0.3
低カルシウム血症	25	2.5	19	0.7
高カリウム血症	23	3.0	20	2.2
プロトロンビン INR 増加	21	2.0	15	2.9
血液				
貧血	43	4.4	79	19
リンパ球減少症	30	7	41	13

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：598～610例、化学療法群：588例～597例。プロトロンビン INR 増加：KEYTRUDA 群：203例、化学療法群：173例。
† Grade 分類は NCI CTCAE v4.03に基づく。

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既治療の非小細胞肺癌

KEYNOTE-010試験は、多施設共同、非盲検、無作為化（1：1：1）、実薬対照の臨床試験であり、プラチナ製剤併用療法を受けた後に疾患進行が認められた非小細胞肺癌患者を対象にKEYTRUDA を投与した際の安全性を評価した。なお、EGFR 感受性遺伝子変異又は ALK 遺伝子転座を有している場合は他の適切な治療法を受けた［臨床試験（14.2）参照］。991例が、KEYTRUDA 2 mg/kg 3週間間隔投与群（339例）、10 mg/kg 3週間間隔投与群（343例）又はドセタキセル 75 mg/m^2 3週間間隔投与群（309例）のいずれかに割り付けられた。自己免疫疾患を合併している患者、全身性副腎皮質ホルモン剤又は免疫抑制剤治療を必要とした患者、又は治験薬初回投与前26週間以内に30 Gy を超える胸部に対する放射線療法を受けていた患者は不適格とされた。

投与期間の中央値は、2 mg/kg 3週間間隔投与群で3.5ヵ月（範囲：1日～22.4ヵ月）、10 mg/kg 3週間間隔投与群で3.5ヵ月（範囲：1日～20.8ヵ月）であった。下記データは6ヵ月以上の投与を受けた、2 mg/kg 3週間間隔投与群の31%の患者で構成している。10 mg/kg 3週間間隔投与群では34%の患者が6ヵ月以上の投与を受けた。

試験集団の背景因子は、年齢の中央値が63歳（範囲：20～88歳）、65歳以上が42%であり、男性の割合は61%、白人が72%、アジア人が21%、局所進行性疾患が8%、転移性疾患が91%であった。脳転移の既往を有していた患者が15%であった。29%の患者が、進行性又は転移性の非小細胞肺癌に対して2種類以上の全身性の他の抗がん剤治療を受けていた。

KEYNOTE-010試験において、KEYTRUDA 2 mg/kg 投与群及び10 mg/kg 投与群の安全性プロファイルは類似していたため、両群を併合解析した（682例）。KEYTRUDA の投与を受けた患者の8%が有害事象により投与を中止した。投与中止に至った主な有害事象は肺臓炎（1.8%）であった。23%の患者が有害事象により KEYTRUDA を休薬し、発現割合が高い（1%以上）有害事象は、下痢（1%）、疲労（1.3%）、肺炎（1%）、肝酵素増加（1.2%）、食欲減退（1.3%）及び肺臓炎（1%）であった。[表 1.6.2-14]及び[表 1.6.2-15]に、KEYNOTE-010試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-14　　有害事象*

KEYTRUDA の投与を受けた非小細胞肺癌患者で発現割合 10%以上（KEYNOTE-010 試験）

有害事象	KEYTRUDA 2 mg/kg 及び10 mg/kg 3週間間隔投与（682例）		ドセタキセル 75 mg/m^2 3週間間隔投与（309例）	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
代謝および栄養障害				
食欲減退	25	1.5	23	2.6
呼吸器、胸郭および縦隔障害				
呼吸困難	23	3.7	20	2.6
咳嗽	19	0.6	14	0
胃腸障害				
悪心	20	1.3	18	0.6
便秘	15	0.6	12	0.6

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嘔吐	13	0.9	10	0.6
皮膚および皮下組織障害				
発疹‡	17	0.4	8	0
そう痒症	11	0	3	0.3
筋骨格系および結合組織障害				
関節痛	11	1.0	9	0.3
背部痛	11	1.5	8	0.3

* 発現割合がドセタキセル投与群と同じ又はドセタキセル投与群よりも高い有害事象
† Grade 分類は NCI CTCAE v4.0に基づく。
‡ 発疹、紅斑性皮疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹及びそう痒性皮疹を含む。

KEYTRUDA を投与された患者で認められたその他の臨床的に重要な有害事象は、疲労（25%）、下痢（14%）、無力症（11%）及び発熱（11%）であった。

表 1.6.2-15　　ベースラインから悪化した臨床検査値異常*
KEYTRUDA の投与を受けた非小細胞肺癌患者で発現割合 20%以上（KEYNOTE-010 試験）

臨床検査†	KEYTRUDA 2 mg/kg 及び10 mg/kg 3週間間隔投与		ドセタキセル 75 mg/m^2 3週間間隔投与	
	All Grades‡ (%)	Grade 3-4 (%)	All Grades‡ (%)	Grade 3-4 (%)
血清生化学				
低ナトリウム血症	32	8	27	2.9
アルカリホスファターゼ増加	28	3.0	16	0.7
AST 増加	26	1.6	12	0.7
ALT 増加	22	2.7	9	0.4

* 発現割合がドセタキセル投与群と同じ又はドセタキセル投与群よりも高い臨床検査値異常
† 各臨床検査値異常の発現割合は、ベースライン時及び治験期間中に1つ以上の臨床検査結果が得られている患者数に基づく：KEYTRUDA（631～638例）、ドセタキセル（274～277例）
‡ Grade 分類は NCI CTCAE v4.0に基づく。

KEYTRUDA の投与を受けた患者の20%以上に発現したその他の臨床検査値異常は、高血糖（All Grades：44%、Grade 3-4：4.1%）、貧血（All Grades：37%、Grade 3-4：3.8%）、高トリグリセリド血症（All Grades：36%、Grade 3-4：1.8%）、リンパ球減少症（All Grades：35%、Grade 3-4：9%）、低アルブミン血症（All Grades：34%、Grade 3-4：1.6%）及び高コレステロール血症（All Grades：20%、Grade 3-4：0.7%）であった。

<u>切除可能な非小細胞肺癌の術前及び術後補助療法</u>

KEYNOTE-671試験は、多施設共同、無作為化（1：1）、二重盲検、プラセボ対照の臨床試験であり未治療かつ AJCC 第8版による II 期、IIIA 期又は IIIB 期（N2）の切除可能な非小細胞肺癌患者を対象に KEYTRUDA とプラチナ製剤化学療法との併用による術前補助療法及びその後の KEYTRUDA 単独療法による術後補助療法における KEYTRUDA の安全性を評価した［臨床試験（14.2）参照］。治療2年以内に全身療法を必要とした活動性の自己免疫疾患を有する患者又は免疫抑制剤治療を必要とした医学的状態の患者は不適格とされた。

KEYTRUDA 200 mg の3週間間隔の投与期間の中央値は10.9ヵ月（範囲：1日～18.6ヵ月）であっ

た。試験集団の背景因子は、年齢の中央値が64歳（範囲：26～83歳）、65歳以上が45%、75歳以上が7%であり、男性の割合は71%、白人が61%、アジア人が31%、黒人が2%、人種未報告が4%、ヒスパニック系又はラテン系が9%であった。

KEYTRUDA とプラチナ製剤化学療法との併用による術前補助療法及びその後の KEYTRUDA 単独療法による術後補助療法を受けた切除可能な非小細胞肺癌患者で認められた有害事象は、腫瘍の種類を問わず他の臨床試験において KEYTRUDA と化学療法を併用する患者で認められたものと概して同様であった。

KEYNOTE-671試験の術前補助療法期

計396例がプラチナ製剤化学療法と併用する術前補助療法として KEYTRUDA の投与を1回以上受け、399例がプラチナ製剤化学療法と併用する術前補助療法としてプラセボの投与を1回以上受けた。

プラチナ製剤化学療法と併用する術前補助療法として KEYTRUDA の投与を受けた患者の34%で重篤な有害事象が発現した。高頻度（2%以上）に認められた重篤な有害事象は、肺炎（4.8%）、静脈血栓塞栓症（3.3%）及び貧血（2%）であった。患者の1.3%で死亡に至る有害事象が発現し、原因不明の死亡（0.8%）、敗血症（0.3%）及び免疫性肺疾患（0.3%）であった。

プラチナ製剤化学療法と併用する術前補助療法として KEYTRUDA の投与を受けた患者の18%が、有害事象により投与を中止した。高頻度（1%以上）に認められた投与中止に至った有害事象は、急性腎障害（1.8%）、間質性肺疾患（1.8%）、貧血（1.5%）、好中球減少症（1.5%）及び肺炎（1.3%）であった。術前補助療法で KEYTRUDA の投与を受けた患者396例及びプラセボの投与を受けた患者399例のうち、それぞれ6%（25例）及び4.3%（17例）が有害事象のため手術を受けなかった。KEYTRUDA 群で手術中止に至った高頻度（1%以上）に認められた有害事象は間質性肺炎（1%）であった。

KEYTRUDA の投与及び手術を受けた患者325例のうち、3.1%（10例）が有害事象のため手術を延期した（術前補助療法の投与が4サイクル未満の場合は、最後に受けた術前補助療法から8週間後以降、術前補助療法が4サイクルの場合は、術前補助療法の初回投与から20週間後以降に手術を実施）。プラセボの投与及び手術を受けた患者317例のうち、2.5%（8例）が有害事象のため手術を延期した。

KEYTRUDA の投与及び手術を受けた患者325例のうち、7%（22例）が有害事象のため術後補助療法を受けなかった。プラセボの投与及び手術を受けた患者317例のうち、3.2%（10例）が有害事象のため術後補助療法を受けなかった。

KEYNOTE-671試験の術後補助療法期

KEYTRUDA 群の患者290例及びプラセボ群の患者267例が1回以上の術後補助療法を受けた。

術後補助療法として KEYTRUDA の単独療法を受けた患者の14%で重篤な有害事象が発現した。

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高頻度に認められた重篤な有害事象は肺炎（3.4%）であった。死亡に至る有害事象として肺出血1件が発現した。患者の12%が有害事象のため術後補助療法としての KEYTRUDA の投与を中止した。術後補助療法としての KEYTRUDA の投与中止に至った高頻度（1%以上）に認められた有害事象は下痢（1.7%）、間質性肺疾患（1.4%）、AST 増加（1%）及び筋骨格痛（1%）であった。

外科的切除後の非小細胞肺癌の術後補助療法

KEYNOTE-091試験は、多施設共同、無作為化（1：1）、三重盲検、プラセボ対照の臨床試験であり外科的完全切除後のIB期（T2a≥4 cm）、II期又はIIIA期の非小細胞癌患者を対象にKEYTRUDAを単独投与した際の安全性を評価した。4サイクルまでの術後化学療法は任意であった［臨床試験（14.2）参照］。計1161例が KEYTRUDA 200 mg（580例）又はプラセボ（581例）を3週間間隔で投与された。活動性の自己免疫疾患を有する患者、慢性的に免疫抑制剤治療を必要とした医学的状態の患者、間質性肺疾患又は肺臓炎の既往歴がある患者は不適格とされた。

KEYTRUDA の投与期間の中央値は11.7ヵ月（範囲：1日～18.9ヵ月）であった。KEYTRUDA 群の68%の患者が6ヵ月以上の KEYTRUDA の投与を受けた。

KEYNOTE-091試験で認められた有害事象は、甲状腺機能低下症（22%）、甲状腺機能亢進症（11%）及び肺臓炎（7%）を除き他の非小細胞肺癌で KEYTRUDA の単独投与を受けた患者で発現した有害事象と概して類似していた。死亡に至る有害事象として心筋炎が2件発現した。

頭頸部扁平上皮癌

転移性又は切除不能な再発頭頸部扁平上皮癌の一次治療

KEYNOTE-048試験は、多施設共同、非盲検、無作為化（1：1：1）、実薬対照の臨床試験であり、未治療の再発又は転移性頭頸部扁平上皮癌患者を対象に、KEYTRUDA を単独投与、並びにプラチナ製剤（シスプラチン又はカルボプラチン）及びフルオロウラシルの化学療法と併用投与した際の安全性を評価した［臨床試験（14.3）参照］。2年以内に全身療法を必要とした自己免疫疾患を有する患者、免疫抑制剤治療を必要とした医学的状態の患者は不適格とされた。KEYTRUDA 200 mg の3週間間隔の単独投与（300例）、又はプラチナ製剤とフルオロウラシルとの3週間間隔の併用投与を6コース後、KEYTRUDA 単独投与（276例）のいずれかの投与を受けた計576例を、セツキシマブ週1回投与及びプラチナ製剤とフルオロウラシルの3週間間隔の併用投与を6コース後、セツキシマブを単独投与した287例と比較した。

投与期間の中央値は、KEYTRUDA 単独投与群で3.5ヵ月（範囲：1日～24.2ヵ月）、KEYTRUDA 併用投与群では5.8ヵ月（範囲：3日～24.2ヵ月）であった。KEYTRUDA 単独投与群で17%、KEYTRUDA 併用投与群で18%の患者が12ヵ月以上の KEYTRUDA の投与を受けた。KEYTRUDA の併用投与を受けている57%の患者がカルボプラチンによる治療を受けた。

KEYTRUDA 単独投与群の患者の12%が有害事象により投与を中止した。KEYTRUDA の投与中止に至った主な有害事象は、敗血症（1.7%）及び肺炎（1.3%）であった。31%の患者が有害事象により KEYTRUDA を休薬し、発現割合が高い（2%以上）有害事象は、肺炎（2.3%）、肺臓炎（2.3%）

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及び低ナトリウム血症（2%）であった。

KEYTRUDA 併用投与群の患者の16%が有害事象により投与を中止した。KEYTRUDA の投与中止に至った主な有害事象は、肺炎（2.5%）、肺臓炎（1.8%）及び敗血症性ショック（1.4%）であった。45%の患者が有害事象により KEYTRUDA を休薬し、発現割合が高い（2%以上）有害事象は、好中球減少症（14%）、血小板減少症（10%）、貧血（6%）、肺炎（4.7%）及び発熱性好中球減少症（2.9%）であった。

[表 1.6.2-16]及び[表 1.6.2-17]に、KEYNOTE-048試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-16　有害事象[*]

KEYTRUDA の投与を受けた頭頸部扁平上皮癌患者で発現割合 10%以上（KEYNOTE-048 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（300例）		KEYTRUDA 200 mg 3週間間隔投与とプラチナ製剤及びフルオロウラシルの併用投与（276例）		セツキシマブ、プラチナ製剤及びフルオロウラシル（287例）	
	All Grades[*] (%)	Grade 3-4 (%)	All Grades[*] (%)	Grade 3-4 (%)	All Grades[*] (%)	Grade 3-4 (%)
一般・全身障害および投与部位の状態						
疲労[†]	33	4	49	11	48	8
発熱	13	0.7	16	0.7	12	0
粘膜の炎症	4.3	1.3	31	10	28	5
胃腸障害						
便秘	20	0.3	37	0	33	1.4
悪心	17	0	51	6	51	6
下痢[‡]	16	0.7	29	3.3	35	3.1
嘔吐	11	0.3	32	3.6	28	2.8
嚥下障害	8	2.3	12	2.9	10	2.1
口内炎	3	0	26	8	28	3.5
皮膚および皮下組織障害						
発疹[§]	20	2.3	17	0.7	70	8
そう痒症	11	0	8	0	10	0.3
呼吸器、胸郭および縦隔障害						
咳嗽[¶]	18	0.3	22	0	15	0
呼吸困難[#]	14	2.0	10	1.8	8	1.0
内分泌障害						
甲状腺機能低下症	18	0	15	0	6	0
代謝および栄養障害						
食欲減退	15	1.0	29	4.7	30	3.5
体重減少	15	2	16	2.9	21	1.4
感染症および寄生虫症						
肺炎[Þ]	12	7	19	11	13	6
神経系障害						
頭痛	12	0.3	11	0.7	8	0.3
浮動性めまい	5	0.3	10	0.4	13	0.3
末梢性感覚ニューロパチー[β]	1	0	14	1.1	7	1
筋骨格系および結合組織障害						
筋肉痛[à]	12	1.0	13	0.4	11	0.3
頚部痛	6	0.7	10	1.1	7	0.7
精神障害						
不眠症	7	0.7	10	0	8	0

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* Grade 分類は NCI CTCAE v4.0に基づく。
† 疲労及び無力症を含む。
‡ 下痢、大腸炎、血性下痢及び顕微鏡的大腸炎を含む。
§ 皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、水疱性皮膚炎、接触皮膚炎、剥脱性皮膚炎、薬疹、紅斑、多形紅斑、発疹、紅斑性皮疹、全身性皮疹、斑状皮疹、斑状丘疹状皮疹、そう痒性皮疹及び脂漏性皮膚炎を含む。
¶ 咳嗽及び湿性咳嗽を含む。
# 呼吸困難及び労作性呼吸困難を含む。
Þ 肺炎、異型肺炎、細菌性肺炎、ブドウ球菌性肺炎、誤嚥性肺炎、下気道感染、肺感染及びシュードモナス性肺感染を含む。
ß 末梢性感覚ニューロパチー、末梢性ニューロパチー、感覚鈍麻及び異常感覚を含む。
à 背部痛、筋骨格系胸痛、筋骨格痛及び筋肉痛を含む。

表 1.6.2-17　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた頭頸部扁平上皮癌患者で発現割合 20%以上（KEYNOTE-048 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与		KEYTRUDA 200 mg 3週間間隔投与とプラチナ製剤及びフルオロウラシルの併用投与		セツキシマブ、プラチナ製剤及びフルオロウラシル	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
血液						
リンパ球減少症	54	25	69	35	74	45
貧血	52	7	89	28	78	19
血小板減少症	12	3.8	73	18	76	18
好中球減少症	7	1.4	67	35	71	42
血清生化学						
高血糖	47	3.8	55	6	66	4.7
低ナトリウム血症	46	17	56	20	59	20
低アルブミン血症	44	3.2	47	4.0	49	1.1
AST 増加	28	3.1	24	2.0	37	3.6
ALT 増加	25	2.1	22	1.6	38	1.8
アルカリホスファターゼ増加	25	2.1	27	1.2	33	1.1
高カルシウム血症	22	4.6	16	4.3	13	2.6
低カルシウム血症	22	1.1	32	4	58	7
高カリウム血症	21	2.8	27	4.3	29	4.3
低リン酸血症	20	5	35	12	48	19
低カリウム血症	19	5	34	12	47	15
クレアチニン増加	18	1.1	36	2.3	27	2.2
低マグネシウム血症	16	0.4	42	1.7	76	6

* 各臨床検査値異常の発現割合は、ベースライン時及び治験期間中に1つ以上の臨床検査結果が得られている患者数に基づく：KEYTRUDA／化学療法（235～266例）、KEYTRUDA（241～288例）、セツキシマブ／化学療法（249～282例）
† Grade 分類は NCI CTCAE v4.0に基づく。

既治療の再発又は転移性頭頸部扁平上皮癌

KEYNOTE-012試験の頭頸部扁平上皮癌患者192例の、KEYTRUDA の投与期間の中央値は3.3ヵ月（範囲：1日～27.9ヵ月）であった［臨床試験（14.3）参照］。KEYNOTE-012試験では、自己免疫性疾患を有する患者、又は免疫抑制剤治療を必要とした患者は不適格とされた。

試験集団の背景因子は、年齢の中央値が60歳（範囲：20～84歳）であり、65歳以上の割合は35%、男性が83%、白人が77%、アジア人が15%、黒人が5%であった。再発又は転移により全身療法を2レジメン以上受けた患者は61%であり、放射線療法の既往は95%であった。ベースライン時のECOG performance status は0（30%）又は1（70%）で、M1の割合は86%であった。

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患者の17%が有害事象により投与を中止した。本剤の投与を受けた患者の45%が重篤な有害事象を発現した。2%以上の患者に報告された高頻度に発現した重篤な有害事象は、肺炎、呼吸困難、錯乱状態、嘔吐、胸水及び呼吸不全であった。重篤な有害事象を含む有害事象の発現割合は、2つの投与スケジュール（10 mg/kg を2週間間隔又は200 mg を3週間間隔）で同様であり、これらの安全性結果の要約を併合した。高頻度に発現した有害事象（20%以上）は、疲労、食欲減退及び呼吸困難であった。頭頸部扁平上皮癌患者に発現した有害事象は、顔面浮腫の発現割合の増加（All Grades : 10%、Grade 3-4 : 2.1%）及び甲状腺機能低下症の新規発症又は悪化を除いては、KEYTRUDAの単独投与を受けた悪性黒色腫又は非小細胞肺癌の2799例で発現した有害事象と同様であった［警告及び使用上の注意（5.1）参照］。

再発又は難治性古典的ホジキンリンパ腫

KEYNOTE-204試験

KEYNOTE-204試験で KEYTRUDA の安全性を評価した［臨床試験（14.4）参照］。再発又は難治性古典的ホジキンリンパ腫を有する成人患者に、KEYTRUDA 200 mg を3週間間隔で静脈内投与（148例）又はブレンツキシマブベドチン（BV）1.8 mg/kg を3週間間隔で静脈内投与（152例）した。試験では、ANC が1000/μL 以上、血小板数が75000/μL 以上、肝トランスアミナーゼが基準値上限（ULN）の2.5倍以下、ビリルビンが ULN の1.5倍以下及び ECOG パフォーマンスステータスが0又は1の患者を適格とした。また、活動性・非感染性肺臓炎、ステロイド投与を要する肺臓炎の既往、活動性の自己免疫疾患、免疫抑制剤による治療を要する医学的状態、又は5年以内に同種造血幹細胞移植を受けた患者は除外した。KEYTRUDA の投与期間の中央値は、10ヵ月（範囲：1日～2.2年）であった。KEYTRUDA の投与期間が6ヵ月以上の患者は68%、1年以上の患者は48%であった。

KEYTRUDA の投与を受けた患者の30%で重篤な副作用が発現した。1%以上に発現した重篤な副作用は、肺臓炎、肺炎、発熱、心筋炎、急性腎障害、発熱性好中球減少症及び敗血症であった。3例（2%）の患者が疾患進行以外の理由（2例が同種造血幹細胞移植後の合併症及び1例が死因不明）で死亡した。

副作用による投与中止は14%の患者で認められた。投与中止例の7%は肺臓炎に起因していた。副作用による休薬は30%の患者で認められた。3%以上の患者で発現した休薬を要する副作用は、上気道感染、肺臓炎、トランスアミナーゼ増加及び肺炎であった。

患者の38%で、全身性副腎皮質ホルモン剤の投与を必要とする副作用が発現した。

[表 1.6.2-18]に KEYNOTE-204試験の有害事象を示す。

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表 1.6.2-18　有害事象*
KEYTRUDA の投与を受けた古典的ホジキンリンパ腫患者で発現割合 10%以上
（KEYNOTE-204 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（148例）		ブレンツキシマブベドチン 1.8 mg/kg 3週間間隔投与（152例）	
	All Grades* (%)	Grades 3- 4 (%)	All Grades* (%)	Grades 3- 4† (%)
感染症および寄生虫症				
上気道感染‡	41	1.4	24	0
尿路感染	11	0	3	0.7
筋骨格系および結合組織				
筋骨格痛§	32	0	29	1.3
胃腸障害				
下痢¶	22	2.7	17	1.3
悪心	14	0	24	0.7
嘔吐	14	1.4	20	0
腹痛#	11	0.7	13	1.3
一般・全身障害および投与部位の状態				
発熱	20	0.7	13	0.7
疲労 Þ	20	0	22	0.7
皮膚および皮下組織障害				
発疹 ß	20	0	19	0.7
そう痒症	18	0	12	0
呼吸器、胸郭および縦隔障害				
咳嗽 à	20	0.7	14	0.7
肺臓炎 è	11	5	3	1.3
呼吸困難 ð	11	0.7	7	0.7
内分泌障害				
甲状腺機能低下症	19	0	3	0
神経系障害				
末梢性ニューロパチー ø	11	0.7	43	7
頭痛 ý	11	0	11	0

* Grade 分類は NCI CTCAE v4.0に基づく。
† BV 群の有害事象は Grade 3のみであった。
‡ 急性副鼻腔炎、上咽頭炎、咽頭炎、咽頭扁桃炎、鼻炎、副鼻腔炎、細菌性副鼻腔炎、扁桃炎、上気道感染及びウイルス性上気道感染を含む。
§ 関節痛、背部痛、骨痛、筋骨格不快感、筋骨格系胸痛、筋骨格痛、筋肉痛、頚部痛、非心臓性胸痛及び四肢痛を含む。
¶ 下痢、胃腸炎、大腸炎及び腸炎を含む。
# 腹部不快感、腹痛、下腹部痛及び上腹部痛を含む。
Þ 疲労及び無力症を含む。
ß ざ瘡様皮膚炎、アトピー性皮膚炎、アレルギー性皮膚炎、接触皮膚炎、剥脱性皮膚炎、乾癬様皮膚炎、湿疹、発疹、紅斑性皮疹、毛孔性皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹及び中毒性皮疹を含む。
à 咳嗽及び湿性咳嗽を含む。
è 肺臓炎及び間質性肺疾患を含む。
ð 呼吸困難、労作性呼吸困難及び喘鳴を含む。
ø 異常感覚、感覚鈍麻、末梢性ニューロパチー、錯感覚、末梢性運動ニューロパチー、末梢性感覚運動ニューロパチー、末梢性感覚ニューロパチー及び多発ニューロパチーを含む。
ý 頭痛、片頭痛及び緊張性頭痛を含む。

KEYTRUDA の投与を受けた患者の10%未満で認められた臨床的に重要な有害事象は、ヘルペスウイルス感染（9%）、肺炎（8%）、口腔咽頭痛（8%）、甲状腺機能亢進症（5%）、過敏症（4.1%）、Infusion reaction（3.4%）、精神状態の変化（2.7%）並びにぶどう膜炎、心筋炎、甲状腺炎、発熱性好中球減少症、敗血症及び腫瘍フレア（それぞれ1.4%）であった。

[表 1.6.2-19]に KEYNOTE-204試験の臨床検査値異常を示す。

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表 1.6.2-19　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた古典的ホジキンリンパ腫患者で発現割合 15%以上
（KEYNOTE-204 試験）

臨床検査値異常*	KEYTRUDA 200 mg 3週間間隔投与		ブレンツキシマブベドチン 1.8 mg/kg 3週間間隔投与	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
血液生化学				
高血糖	46	4.1	36	2.0
AST 増加	39	5	41	3.9
ALT 増加	34	6	45	5
低リン酸血症	31	5	18	2.7
クレアチニン増加	28	3.4	14	2.6
低マグネシウム血症	25	0	12	0
低ナトリウム血症	24	4.1	20	3.3
低カルシウム血症	22	2.0	16	0
アルカリホスファターゼ増加	21	2.1	22	2.6
高ビリルビン血症	16	2.0	9	1.3
低アルブミン血症	16	0.7	19	0.7
高カリウム血症	15	1.4	8	0
血液				
リンパ球減少症	35	9	32	13
血小板減少症	34	10	26	5
好中球減少症	28	8	43	17
貧血	24	5	33	8

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：143～148例、ブレンツキシマブベドチン群：146～152例。低マグネシウム血症については KEYTRUDA 群53例、ブレンツキシマブベドチン群50例。
† Grade 分類は NCI CTCAE v4.0に基づく。

KEYNOTE-087試験

KEYNOTE-087試験において、KEYTRUDA の投与を受けた古典的ホジキンリンパ腫患者210例の KEYTRUDA の投与期間の中央値は8.4ヵ月（範囲：1日～15.2ヵ月）であった［臨床試験（14.4）参照］。KEYTRUDA の投与を受けた患者の16%が重篤な有害事象を発現した。患者の1%以上に発現した重篤な有害事象は、肺炎、肺臓炎、発熱、呼吸困難、移植片対宿主病（GVHD）及び帯状疱疹であった。2例の患者が疾患進行以外の理由（1例が同種造血幹細胞移植後の移植片対宿主病及び1例が敗血症性ショック）で死亡した。

副作用による投与中止は5%の患者で認められ、休薬は26%の患者で認められた。全身性副腎皮質ホルモン剤の投与を必要とした患者は15%であった。[表　1.6.2-20]及び[表　1.6.2-21]に KEYNOTE-087試験の有害事象及び臨床検査値異常を示す。

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表 1.6.2-20　有害事象

KEYTRUDA の投与を受けた古典的ホジキンリンパ腫患者で発現割合 10%以上

（KEYNOTE-087 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（210例）	
	All Grades* (%)	Grade 3 (%)
一般・全身障害および投与部位の状態		
疲労†	26	1.0
発熱	24	1.0
呼吸器、胸郭および縦隔障害		
咳嗽‡	24	0.5
呼吸困難§	11	1.0
筋骨格系および結合組織障害		
筋骨格痛¶	21	1.0
関節痛	10	0.5
胃腸障害		
下痢#	20	1.4
嘔吐	15	0
悪心	13	0
皮膚および皮下組織障害		
発疹 Þ	20	0.5
そう痒症	11	0
内分泌障害		
甲状腺機能低下症	14	0.5
感染症および寄生虫症		
上気道感染	13	0
神経系障害		
頭痛	11	0.5
末梢性ニューロパチーβ	10	0

* Grade 分類は NCI CTCAE v4.0に基づく。
†疲労及び無力症を含む。
‡咳嗽及び湿性咳嗽を含む。
§呼吸困難、労作性呼吸困難及び喘鳴を含む。
¶背部痛、筋肉痛、骨痛、筋骨格痛、四肢痛、筋骨格系胸痛、筋骨格不快感及び頚部痛を含む。
#下痢、胃腸炎、大腸炎及び腸炎を含む。
Þ発疹、斑状丘疹状皮疹、薬疹、湿疹、皮脂欠乏性湿疹、皮膚炎、ざ瘡様皮膚炎、接触皮膚炎、紅斑性皮疹、斑状皮疹、丘疹性皮疹、そう痒性皮疹、脂漏性皮膚炎及び乾癬様皮膚炎を含む。
β末梢性ニューロパチー、末梢性感覚ニューロパチー、感覚鈍麻、錯感覚、異常感覚及び多発ニューロパチーを含む。

KEYTRUDA の投与を受けた患者の10%未満で認められた臨床的に重要な有害事象は、Infusion reaction（9%）、甲状腺機能亢進症（3%）、肺臓炎（3%）、ぶどう膜炎及び筋炎（それぞれ1%）、並びに脊髄炎及び心筋炎（それぞれ0.5%）であった。

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表 1.6.2-21　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた古典的ホジキンリンパ腫患者で発現割合 15%以上
（KEYNOTE-087 試験）

臨床検査値異常*	KEYTRUDA 200 mg 3週間間隔投与	
	All Grades† (%)	Grade 3-4 (%)
血清生化学		
高トランスアミナーゼ血症‡	34	2
アルカリホスファターゼ増加	17	0
クレアチニン増加	15	0.5
血液		
貧血	30	6
血小板減少症	27	4
好中球減少症	24	7

*各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：208～209例。
†Grade 分類は NCI CTCAE v4.0に基づく。
‡AST 又は ALT 増加を含む。

KEYNOTE-087試験において、患者の15%未満で高ビリルビン血症（All Grades : 10%、Grade 3-4 : 2.4%）が発現した。

原発性縦隔大細胞型 B 細胞リンパ腫

KEYNOTE-170試験では、KEYTRUDA の投与を受けた原発性縦隔大細胞型 B 細胞リンパ腫患者53例の KEYTRUDA の投与期間の中央値は3.5ヵ月（範囲：1日～22.8ヵ月）であった［臨床試験（14.5）参照］。患者の26%が重篤な有害事象を発現した。患者の2%超で発現した重篤な有害事象は不整脈（4%）、心タンポナーデ（2%）、心筋梗塞（2%）、心嚢液貯留（2%）及び心膜炎（2%）であった。6例（11%）の患者が、投与開始後30日以内に死亡した。副作用による投与中止は8%の患者で認められ、休薬は15%の患者で認められた。全身性副腎皮質ホルモン剤の投与を必要とした患者は25%であった。[表 1.6.2-22]及び[表 1.6.2-23]に KEYNOTE-170試験の有害事象及び臨床検査値異常を示す。

表 1.6.2-22　有害事象
KEYTRUDA の投与を受けた原発性縦隔大細胞型 B 細胞リンパ腫患者で発現割合 10%以上
（KEYNOTE-170 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（53例）	
	All Grades* (%)	Grade 3-4 (%)
筋骨格系および結合組織障害		
筋骨格痛†	30	0
感染症および寄生虫症		
上気道感染‡	28	0

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一般・全身障害および投与部位の状態		
発熱	28	0
疲労§	23	2
呼吸器、胸郭および縦隔障害		
咳嗽¶	26	2
呼吸困難	21	11
胃腸障害		
下痢#	13	2
腹痛Þ	13	0
悪心	11	0
心臓障害		
不整脈β	11	4
神経系障害		
頭痛	11	0

*Grade 分類は NCI CTCAE v4.0に基づく。
†関節痛、背部痛、筋肉痛、筋骨格痛、四肢痛、筋骨格系胸痛、骨痛、頚部痛及び非心臓性胸痛を含む。
‡上咽頭炎、咽頭炎、鼻漏、鼻炎、副鼻腔炎及び上気道感染を含む。
§疲労及び無力症を含む。
¶アレルギー性咳嗽、咳嗽及び湿性咳嗽を含む。
#下痢及び胃腸炎を含む。
Þ腹痛及び上腹部痛を含む。
β心房細動、洞性頻脈、上室性頻脈及び頻脈を含む。

KEYTRUDA の投与を受けた患者の10%未満で認められた臨床的に重要な有害事象は、甲状腺機能低下症（8%）、甲状腺機能亢進症及び心膜炎（それぞれ4%）、甲状腺炎、心嚢液貯留、肺臓炎、関節炎及び急性腎障害（それぞれ2%）であった。

表 1.6.2-23　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた原発性縦隔大細胞型 B 細胞リンパ腫患者で発現割合 15%以上
（KEYNOTE-170 試験）

臨床検査値異常*	KEYTRUDA 200 mg 3週間間隔投与	
	All Grades† (%)	Grade 3-4 (%)
血液		
貧血	47	0
白血球減少症	35	9
リンパ球減少症	32	18
好中球減少症	30	11
血清生化学		
高血糖	38	4
低リン酸血症	29	10
高トランスアミナーゼ血症‡	27	4
低血糖	19	0
アルカリホスファターゼ増加	17	0
クレアチニン増加	17	0
低カルシウム血症	15	4
低カリウム血症	15	4

*各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：44～48例。
†Grade 分類は NCI CTCAE v4.0に基づく。
‡AST 又は ALT 増加を含む。

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尿路上皮癌

尿路上皮癌に対するエンホルツマブベドチンとの併用

KEYNOTE-A39試験では、局所進行性又は転移性の尿路上皮癌患者を対象に、KEYTRUDA をエンホルツマブベドチンと併用投与した場合の安全性を評価した［臨床試験（14.6）参照］。計440例に対して、各コース（21日間）の1日目に KEYTRUDA 200 mg 及び1日目と8日目にエンホルツマブベドチン1.25 mg/kg を投与し、比較対象として433例に各コース（21日間）の1日目と8日目にゲムシタビン及び1日目に治験担当医師が選択したシスプラチン又はカルボプラチンを投与した。KEYTRUDA とエンホルツマブベドチンとの併用投与における KEYTRUDA の投与期間の中央値は8.5ヵ月（範囲：9日～28.5ヵ月）であった。

KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた患者の3.9%で、死亡に至った有害事象が発現した。このうち、急性呼吸不全（0.7%）、肺炎（0.5%）、及び肺臓炎／間質性肺疾患（0.2%）であった。

KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた患者の50%で、重篤な有害事象が発現した。KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた患者の2%以上で認められた重篤な有害事象は、発疹（6%）、急性腎障害（5%）、肺臓炎／間質性肺疾患（4.5%）、尿路感染（3.6%）、下痢（3.2%）、肺炎（2.3%）、発熱（2%）、及び高血糖（2%）であった。

患者の27%が KEYTRUDA の投与を中止した。KEYTRUDA の投与中止に至った主な有害事象（2%以上）は、肺臓炎／間質性肺疾患（4.8%）及び発疹（3.4%）であった。

患者の61%が KEYTRUDA を休薬した。KEYTRUDA の休薬に至った主な有害事象（2%以上）は、発疹（17%）、末梢性ニューロパチー（7%）、COVID-19（5%）、下痢（4.3%）、肺臓炎／間質性肺疾患（3.6%）、好中球減少症（3.4%）、疲労（3%）、アラニンアミノトランスフェラーゼ増加（2.7%）、高血糖（2.5%）、肺炎（2%）、及びそう痒症（2%）であった。

[表 1.6.2-24]及び[表 1.6.2-25]に KEYNOTE-A39試験で KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-24　有害事象
KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた尿路上皮癌患者で
発現割合 20%以上（All Grades）（KEYNOTE- A39 試験）

有害事象	KEYTRUDA とエンホルツマブベドチンとの併用投与（440例）		化学療法（433例）	
	All Grades*（%）	Grades 3-4（%）	All Grades*（%）	Grades 3-4（%）
皮膚および皮下組織障害				
発疹†	68	15	15	0
そう痒症	41	1.1	7	0
脱毛症	35	0.5	8	0.2
一般・全身障害および投与部位の状態				
疲労†	51	6	57	7

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神経系障害				
末梢性ニューロパチー†	67	8	14	0
味覚不全	21	0	9	0
代謝および栄養障害				
食欲減退	33	1.8	26	1.8
胃腸障害				
下痢	38	4.5	16	1.4
悪心	26	1.6	41	2.8
便秘	26	0	34	0.7
臨床検査				
体重減少	33	3.6	9	0.2
眼障害				
ドライアイ†	24	0	2.1	0
感染症および寄生虫症				
尿路感染	21	5	19	8

* Grade 分類は NCI CTCAE v4.03に基づく。
† 複数の用語を含む。

20%未満で認められた臨床的に重要な有害事象は、発熱（18%）、皮膚乾燥（17%）、嘔吐（12%）、肺臓炎／間質性肺疾患（10%）、甲状腺機能低下症（10%）、霧視（6%）、注入部位血管外漏出（2%）、及び筋炎（0.5%）であった。

表 1.6.2-25　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた尿路上皮癌患者で発現割合 20%以上（KEYNOTE-A39 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔とエンホルツマブベドチンとの併用		化学療法	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
血清生化学				
アスパラギン酸アミノトランスフェラーゼ増加	75	4.6	39	3.3
クレアチニン増加	71	3.2	68	2.6
高血糖	66	14	54	4.7
アラニンアミノトランスフェラーゼ増加	59	5	49	3.3
低ナトリウム血症	46	13	47	13
低リン血症	44	9	36	9
低アルブミン血症	39	1.8	35	0.5
低カリウム血症	26	5	16	3.1
高カリウム血症	24	1.4	36	4.0
高カルシウム血症	21	1.2	14	0.2
血液				
リンパ球数減少	58	15	59	17
貧血	53	7	89	33
好中球減少症	30	9	80	50

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：407～439例。
† Grade 分類は NCI CTCAE v4.03に基づく。

シスプラチン不耐容の尿路上皮癌に対するエンホルツマブベドチンとの併用

シスプラチン併用化学療法に不耐容の局所進行性又は転移性の尿路上皮癌患者を対象とした

KEYNOTE-869試験で、エンホルツマブベドチンとの併用による KEYTRUDA の安全性が評価された［臨床試験（14.6）参照］。計121例の患者は、各コース（21日間）の1日目に KEYTRUDA 200 mg、1日目及び8日目にエンホルツマブベドチン1.25 mg/kg を投与された。KEYTRUDA の投与期間の中央値は6.9ヵ月（範囲：1日～29.6ヵ月）であった。

KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた患者の5%で、死亡に至った有害事象が発現した。その内訳は、敗血症（1.6%）、水疱性皮膚炎（0.8%）、重症筋無力症（0.8%）及び肺臓炎（0.8%）であった。

KEYTRUDA とエンホルツマブベドチンの併用投与を受けた患者の50%で、重篤な有害事象が発現した。KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた患者の2%以上に報告された重篤な有害事象は、急性腎障害（7%）、尿路感染（7%）、尿路性敗血症（5%）、血尿（3.3%）、肺炎（3.3%）、肺臓炎（3.3%）、敗血症（3.3%）、貧血（2.5%）、下痢（2.5%）、低血圧（2.5%）、重症筋無力症（2.5%）、筋炎（2.5%）及び尿閉（2.5%）であった。

患者の32%が KEYTRUDA の投与を中止した。高頻度に認められた（2%以上）KEYTRUDA の投与中止に至った有害事象は、肺臓炎（5%）、末梢性ニューロパチー（5%）、発疹（3.3%）及び重症筋無力症（2.5%）であった。

患者の69%が KEYTRUDA を休薬した。高頻度に認められた（2%以上）KEYTRUDA の休薬に至った有害事象は、末梢性ニューロパチー（22%）、発疹（17%）、好中球減少症（7%）、疲労（6%）、下痢（5%）、リパーゼ増加（5%）、急性腎障害（3.3%）、ALT 増加（2.5%）及び COVID-19（2.5%）であった。

[表 1.6.2-26]及び[表 1.6.2-27]に KEYNOTE-869試験で KEYTRUDA とエンホルツマブベドチンの併用投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-26　　有害事象

KEYTRUDA とエンホルツマブベドチンの併用投与を受けた尿路上皮癌患者で発現割合 20%以上

（KEYNOTE-869 試験）

有害事象	KEYTRUDA とエンホルツマブベドチンの併用投与（121例）	
	All Grades*（%）	Grade 3-4（%）
皮膚および皮下組織障害		
発疹†	71	21
脱毛症	52	0
そう痒症	40	3.3
皮膚乾燥	21	0.8
神経系障害		
末梢性ニューロパチー‡	65	3.3
味覚不全	35	0
浮動性めまい	23	0
一般・全身障害および投与部位の状態		
疲労	60	11

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末梢性浮腫	26	0
臨床検査		
体重減少	48	5
胃腸障害		
下痢	45	7
悪心	36	0.8
便秘	27	0
代謝および栄養障害		
食欲減退	38	0.8
感染症および寄生虫症		
尿路感染	30	12
眼障害		
ドライアイ	25	0
筋骨格系および結合組織障害		
関節痛	23	1.7

* Grade 分類は NCI CTCAE v4.03に基づく。
† 水疱、結膜炎、皮膚炎、水疱性皮膚炎、全身性剥脱性皮膚炎、紅斑、多形紅斑、剥脱性発疹、手掌・足底発赤知覚不全症候群、類天疱瘡、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、小水疱性皮疹、皮膚剥脱及び口内炎を含む。
‡ 異常感覚、感覚鈍麻、筋力低下、錯感覚、末梢性運動ニューロパチー、末梢性感覚運動ニューロパチー、末梢性感覚ニューロパチー及び歩行障害を含む。

20%未満で認められた臨床的に重要な有害事象は、嘔吐（19.8%）、発熱（18%）、甲状腺機能低下症（11%）、肺臓炎／間質性肺疾患（10%）、筋炎（3.3%）、重症筋無力症（2.5%）及び注入部位溢出（0.8%）であった。

表 1.6.2-27　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた患者で発現割合 20%以上（KEYNOTE-869 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔とエンホルツマブベドチンの併用	
	All Grades† (%)	Grades 3-4 (%)
血清生化学		
高血糖	74	13
アスパラギン酸アミノトランスフェラーゼ増加	73	9
クレアチニン増加	69	3.3
低ナトリウム血症	60	19
アラニンアミノトランスフェラーゼ増加	60	7
リパーゼ増加	59	32
低アルブミン血症	59	4.2
低リン酸血症	51	15
低カリウム血症	35	8
カリウム増加	27	1.7
カルシウム増加	27	4.2
血液		
貧血	69	15
リンパ球減少症	64	17
好中球減少症	32	12

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：114～121例。
† Grade 分類は NCI CTCAE v4.03に基づく。

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プラチナ製剤不耐容の尿路上皮癌

KEYNOTE-052試験は、何らかの併存疾患を有する局所進行性又は転移性尿路上皮癌患者370例を組み入れ、KEYTRUDA を投与した際の安全性を評価する単群デザインの臨床試験であった。自己免疫疾患を有する患者、又は全身性の副腎皮質ホルモン剤若しくは他の免疫抑制剤による治療を必要とした患者は不適格とした［臨床試験（14.6）参照］。患者は疾患進行又は許容できない副作用が発現するまで、KEYTRUDA を200 mg 3週間間隔で投与された。

KEYTRUDA の投与期間の中央値は2.8ヵ月（範囲：1日～15.8ヵ月）であった。

患者の11%が有害事象により KEYTRUDA の投与を中止した。18例（5%）が疾患進行以外の理由で死亡した。KEYTRUDA の投与を受けた5例（1.4%）が死亡に至った敗血症を発現し、3例（0.8%）が死亡に至った肺炎を発現した。患者の22%が有害事象により KEYTRUDA を休薬した。高頻度に認められた（1%以上）有害事象は、肝酵素増加、下痢、尿路感染、急性腎障害、疲労、関節痛及び肺炎であった。患者の42%が重篤な有害事象を発現した。高頻度に認められた（2%以上）重篤な有害事象は、尿路感染、血尿、急性腎障害、肺炎及び尿路性敗血症であった。

患者の8%にグルココルチコイドによる全身療法を必要とした免疫関連の有害事象、患者の8%にホルモン補充療法を必要とした免疫関連の有害事象が発現した。患者の5%が40 mg 以上のステロイド投与（プレドニゾロン経口換算）を1回以上必要とした。

[表 1.6.2-28]に KEYNOTE-052試験で KEYTRUDA の投与を受けた患者の有害事象を示す。

表 1.6.2-28　有害事象
KEYTRUDA の投与を受けた尿路上皮癌患者で発現割合 10%以上（KEYNOTE-052 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（370例）	
	All Grades* (%)	Grade 3-4 (%)
一般・全身障害および投与部位の状態		
疲労†	38	6
発熱	11	0.5
体重減少	10	0
筋骨格系および結合組織障害		
筋骨格痛‡	24	4.9
関節痛	10	1.1
代謝および栄養障害		
食欲減退	22	1.6
低ナトリウム血症	10	4.1
胃腸障害		
便秘	21	1.1
下痢§	20	2.4
悪心	18	1.1
腹痛¶	18	2.7
肝機能検査数値上昇#	13	3.5
嘔吐	12	0

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皮膚および皮下組織障害		
発疹[Þ]	21	0.5
そう痒症	19	0.3
末梢性浮腫[ß]	14	1.1
感染症および寄生虫症		
尿路感染	19	9
血液およびリンパ系障害		
貧血	17	7
呼吸器、胸郭および縦隔障害		
咳嗽	14	0
呼吸困難	11	0.5
腎および尿路障害		
血中クレアチニン増加	11	1.1
血尿	13	3.0

[*] Grade 分類は NCI CTCAE v4.0に基づく。
[†]疲労及び無力症を含む。
[‡]背部痛、骨痛、筋骨格系胸痛、筋骨格痛、筋肉痛、頚部痛、四肢痛及び脊椎痛を含む。
[§]下痢、大腸炎、腸炎、胃腸炎及び排便回数増加を含む。
[¶]腹痛、骨盤痛、側腹部痛、下腹部痛、腫瘍疼痛、膀胱痛、肝臓痛、恥骨上痛、腹部不快感及び上腹部痛を含む。
[#]自己免疫性肝炎、肝炎、中毒性肝炎、肝損傷、トランスアミナーゼ上昇、高ビリルビン血症、血中ビリルビン増加、ALT 増加、AST 増加、肝酵素増加及び肝機能検査値上昇を含む。
[Þ]皮膚炎、水疱性皮膚炎、湿疹、紅斑、発疹、斑状皮疹、斑状丘疹状皮疹、そう痒性皮疹、膿疱性皮疹、皮膚反応、ざ瘡様皮膚炎、脂漏性皮膚炎、手掌・足底発赤知覚不全症候群及び全身性皮疹を含む。
[ß]末梢性浮腫及び末梢腫脹を含む。

既治療の尿路上皮癌

KEYNOTE-045試験では、プラチナ製剤併用化学療法後に進行した局所進行性又は転移性尿路上皮癌患者を対象に KEYTRUDA を投与した際の安全性を評価した。KEYNOTE-045試験は、多施設、非盲検、無作為化（1：1）、実薬対照の臨床試験であり、患者は KEYTRUDA を200 mg 3週間間隔投与（266例）又は治験担当医師が選択した化学療法［255例（パクリタキセルが84例、ドセタキセルが84例及び vinflunine が87例）］の投与を受けた［臨床試験（14.6）参照］。自己免疫疾患を有する患者又は全身性の副腎皮質ホルモン剤若しくは他の免疫抑制剤による治療を必要とした患者は不適格とした。

投与期間の中央値は、KEYTRUDA の投与を受けた患者で3.5ヵ月（範囲：1日～20ヵ月）及び化学療法の投与を受けた患者で1.5ヵ月（範囲：1日～14ヵ月）であった。

患者の8%が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた投与中止に至った有害事象は、肺臓炎（1.9%）であった。患者の20%が有害事象により KEYTRUDA を休薬し、高頻度に認められた（1%以上）有害事象は、尿路感染（1.5%）、下痢（1.5%）及び大腸炎（1.1%）であった。KEYTRUDA の投与を受けた患者の39%が重篤な有害事象を発現した。KEYTRUDA の投与を受けた患者で高頻度に認められた（2%以上）重篤な有害事象は、尿路感染、肺炎、貧血、及び肺臓炎であった。

[表 1.6.2-29]及び[表 1.6.2-30]に KEYNOTE-045試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

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表 1.6.2-29　有害事象

KEYTRUDA の投与を受けた尿路上皮癌患者で発現割合 10%以上（KEYNOTE-045 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（266例）		化学療法*（255例）	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
一般・全身障害および投与部位の状態				
疲労‡	38	4.5	56	11
発熱	14	0.8	13	1.2
筋骨格系および結合組織障害				
筋骨格痛§	32	3.0	27	2.0
皮膚および皮下組織障害				
そう痒症	23	0	6	0.4
発疹¶	20	0.4	13	0.4
胃腸障害				
悪心	21	1.1	29	1.6
便秘	19	1.1	32	3.1
下痢#	18	2.3	19	1.6
嘔吐	15	0.4	13	0.4
腹痛	13	1.1	13	2.7
代謝および栄養障害				
食欲減退	21	3.8	21	1.2
感染症および寄生虫症				
尿路感染	15	4.9	14	4.3
呼吸器、胸郭および縦隔障害				
咳嗽 Þ	15	0.4	9	0
呼吸困難 ß	14	1.9	12	1.2
腎および尿路障害				
血尿 à	12	2.3	8	1.6

*化学療法：パクリタキセル、ドセタキセル又は vinflunine
†Grade 分類は NCI CTCAE v4.0に基づく。
‡無力症、疲労、倦怠感及び嗜眠を含む。
§背部痛、筋肉痛、骨痛、筋骨格痛、四肢痛、筋骨格系胸痛、筋骨格不快感及び頚部痛を含む。
¶斑状丘疹状皮疹、発疹、性器発疹、紅斑性皮疹、丘疹性皮疹、そう痒性皮疹、膿疱性皮疹、紅斑、薬疹、湿疹、皮脂欠乏性湿疹、接触皮膚炎、ざ瘡様皮膚炎、皮膚炎、脂漏性角化症及び苔癬様角化症を含む。
#下痢、胃腸炎、大腸炎及び腸炎を含む。
Þ咳嗽、湿性咳嗽を含む。
ß呼吸困難、労作性呼吸困難及び喘鳴を含む。
à尿中血陽性、血尿、着色尿を含む。

表 1.6.2-30　ベースラインから悪化した臨床検査値異常

KEYTRUDA の投与を受けた尿路上皮癌患者で発現割合 20%以上（KEYNOTE-045 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与		化学療法	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
血清生化学				
高血糖	52	8	60	7
貧血	52	13	68	18
リンパ球減少症	45	15	53	25
低アルブミン血症	43	1.7	50	3.8
低ナトリウム血症	37	9	47	13
アルカリホスファターゼ増加	37	7	33	4.9
クレアチニン増加	35	4.4	28	2.9
低リン酸血症	29	8	34	14
AST 増加	28	4.1	20	2.5

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高カリウム血症	28	0.8	27	6
低カルシウム血症	26	1.6	34	2.1

*各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA 群：240例～248例、化学療法群：238例～244例。血中リン減少については、KEYTRUDA 群：232例、化学療法群：222例。
†Grade 分類は NCI CTCAE v4.0に基づく。

BCG 療法不応性の高リスク筋層非浸潤性膀胱癌（NMIBC）

KEYNOTE-057試験は、多施設、非盲検、単群の臨床試験であり、KEYTRUDA を投与した際の安全性を評価した。高リスク NMIBC 患者148例が組み入れられ、そのうち96例が乳頭状腫瘍の有無によらない､BCG 療法不応性の CIS を有する患者であった｡患者は許容できない副作用の発現、高リスク NMIBC の持続若しくは再発、疾患進行又は最長24ヵ月まで KEYTRUDA を200 mg 3週間間隔で投与された。

KEYTRUDA の投与期間の中央値は4.3ヵ月（範囲：1日～25.6ヵ月）であった。

患者の11%が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた（1%超）投与中止に至った有害事象は、肺臓炎（1.4%）であった。患者の22%が有害事象により KEYTRUDA を休薬し、高頻度に認められた（2%以上）有害事象は、下痢（4%）及び尿路感染（2%）であった。KEYTRUDA の投与を受けた患者の28%が重篤な有害事象を発現した。KEYTRUDA の投与を受けた患者で高頻度に認められた（2%以上）重篤な有害事象は、肺炎（3%）、心虚血（2%）、大腸炎（2%）、肺塞栓症（2%）、敗血症（2%）及び尿路感染（2%）であった。[表 1.6.2-31]及び[表 1.6.2-32]に KEYNOTE-057試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-31　　有害事象
KEYTRUDA の投与を受けた BCG 療法不応性の高リスク NMIBC 患者で発現割合 10%以上
（KEYNOTE-057 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（148例）	
	All Grades* (%)	Grade 3-4 (%)
一般・全身障害および投与部位の状態		
疲労†	29	0.7
末梢性浮腫‡	11	0
胃腸障害		
下痢§	24	2.0
悪心	13	0
便秘	12	0
皮膚および皮下組織障害		
発疹¶	24	0.7
そう痒症	19	0.7
筋骨格系および結合組織障害		
筋骨格痛#	19	0
関節痛	14	1.4

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腎および尿路障害		
血尿	19	1.4
呼吸器、胸郭および縦隔障害		
咳嗽 [Þ]	19	0
感染症および寄生虫症		
尿路感染	12	2.0
上咽頭炎	10	0
内分泌障害		
甲状腺機能低下症	11	0

[*] Grade 分類は NCI CTCAE v4.03に基づく。
[†]無力症、疲労及び倦怠感を含む。
[‡]末梢性浮腫及び末梢腫脹を含む。
[§]下痢、胃腸炎及び大腸炎を含む。
[¶]斑状丘疹状皮疹、発疹、紅斑性皮疹、そう痒性皮疹、膿疱性皮疹、紅斑、湿疹、皮脂欠乏性湿疹、苔癬様角化症、蕁麻疹及び皮膚炎を含む。
[#]背部痛、筋肉痛、筋骨格痛、四肢痛、筋骨格系胸痛及び頚部痛を含む。
[Þ]咳嗽及び湿性咳嗽を含む。

表 1.6.2-32　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた BCG 療法不応性の高リスク NMIBC 患者で発現割合 20%以上
（KEYNOTE-057 試験）

臨床検査[*]	KEYTRUDA 200 mg 3週間間隔投与	
	All Grades[†] (%)	Grade 3-4 (%)
血清生化学		
高血糖	59	8
ALT 増加	25	3.4
低ナトリウム血症	24	7
低リン酸血症	24	6
低アルブミン血症	24	2.1
高カリウム血症	23	1.4
低カルシウム血症	22	0.7
AST 増加	20	3.4
クレアチニン増加	20	0.7
血液		
貧血	35	1.4
リンパ球減少症	29	1.6

[*] 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：124～147例。
[†] Grade 分類は NCI CTCAE v4.03に基づく。

MSI-High 又は MMR 欠損の癌

KEYNOTE-158試験、KEYNOTE-164試験、KEYNOTE-051試験において MSI-High 又は MMR 欠損の癌患者504例を対象に、KEYTRUDA の安全性が評価された［臨床試験（14.7）参照］。KEYTRUDA 投与期間の中央値は6.2ヵ月（範囲：1日～53.5ヵ月）であった。MSI-High 又は MMR 欠損の癌患者に発現した有害事象は、KEYTRUDA の単独投与を受けた他の固形がん患者で発現した有害事象と同様であった。

MSI-High 又は MMR 欠損の結腸・直腸癌

KEYNOTE-177試験において、MSI-High 又は MMR 欠損の結腸・直腸癌患者153例の KEYTRUDA

投与期間の中央値は11.1ヵ月（範囲：1日～30.6ヵ月）であった［臨床試験（14.8）参照］。自己免疫疾患を有する患者又は免疫抑制剤による治療を必要とした医学的状態の患者は不適格とされた。MSI-High 又は MMR 欠損の結腸・直腸癌患者に発現した有害事象は、KEYTRUDA の単独投与を受けた悪性黒色腫又は非小細胞肺癌の2799例で発現した有害事象と同様であった。

胃癌

局所進行の切除不能又は転移性の HER2陽性胃腺癌又は食道胃接合部腺癌の一次治療

KEYNOTE-811試験では、HER2陽性胃癌又は食道胃接合部癌患者433例を対象として、KEYTRUDA 200 mg、トラスツズマブ及び CAPOX（189例）又は FP（28例）を3週間間隔で投与された217例とプラセボ、トラスツズマブ及び CAPOX（187例）又は FP（29例）を3週間間隔で投与された216例を比較して KEYTRUDA の安全性を評価した［臨床試験（14.9）参照］。

KEYTRUDA の投与期間の中央値は、5.8ヵ月（範囲：1日～17.7ヵ月）であった。

試験集団の背景因子は、年齢の中央値が63歳（範囲：19～84歳）、65歳以上が43%、男性の割合が81%、白人が58%、アジア人が35%、黒人が0.9%、ECOG PS が0の患者が44%及び ECOG PS が1の患者が56%であった。

各群の患者の6%が有害事象により KEYTRUDA 又はプラセボの投与を中止した。KEYTRUDA の投与中止に至った主な有害事象は肺臓炎（1.4%）であった。58%の患者が有害事象により KEYTRUDA を休薬した。休薬に至った発現割合が高い（2%以上）有害事象又は臨床検査値異常は、好中球減少症（18%）、血小板減少症（12%）、下痢（6%）、貧血（3.7%）、低カリウム血症（3.7%）、疲労／無力症（3.2%）、食欲減退（3.2%）、AST 増加（2.8%）、血中ビリルビン増加（2.8%）、肺炎（2.8%）、ALT 増加（2.3%）及び嘔吐（2.3%）であった。

KEYTRUDA 群とプラセボ群を比較したところ、KEYTRUDA を投与された患者と標準治療を受けた患者で発現割合に5%以上の差が認められた有害事象は、下痢（53% vs 44%）及び悪心（49% vs 44%）であった。Grade 3-4の有害事象の発現割合に臨床的に意味のある群間差は認められなかった。

KEYTRUDA を投与された患者と標準治療を受けた患者で発現割合に5%以上の差が認められた臨床検査値異常は、ALT 増加（34% vs 29%）及びクレアチニン増加（20% vs 10%）であった。Grade 3-4の臨床検査値異常の発現割合に臨床的に意味のある群間差は認められなかった。

局所進行の切除不能又は転移性の HER2陰性胃腺癌又は食道胃接合部腺癌の一次治療

KEYNOTE-859試験では、HER2陰性胃癌又は食道胃接合部癌患者1572例を対象として、KEYTRUDA 200 mg 及び FP（106例）又は CAPOX（674例）を3週間間隔で投与された785例とプラセボ及び FP（107例）又は CAPOX（679例）を3週間間隔で投与された787例を比較して KEYTRUDA の安全性を評価した［臨床試験（14.9）参照］。

KEYTRUDA の投与期間の中央値は、6.2ヵ月（範囲：1日～33.7ヵ月）であった。

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KEYTRUDA の投与を受けた患者の45%が重篤な有害事象を発現した。患者の2%超で認められた重篤な有害事象は、肺炎（4.1%）、下痢（3.9%）、出血（3.9%）、及び嘔吐（2.4%）であった。KEYTRUDA の投与を受けた患者の8%で死亡に至った有害事象が発現し、その内訳は、感染症（2.3%）及び血栓塞栓症（1.3%）であった。

患者の15%が有害事象により KEYTRUDA の投与を中止した。KEYTRUDA の投与中止に至った発現割合1%以上の有害事象は、感染症（1.8%）及び下痢（1.0%）であった。

患者の65%が有害事象により KEYTRUDA を休薬した。KEYTRUDA の休薬に至った発現割合2%以上の有害事象又は臨床検査値異常は、好中球減少症（21%）、血小板減少症（13%）、下痢（5.5%）、疲労（4.8%）、感染症（4.8%）、貧血（4.5%）、AST 増加（4.3%）、ALT 増加（3.8%）、血中ビリルビン増加（3.3%）、白血球数減少（2.2%）、悪心（2%）、手掌・足底発赤知覚不全症候群（2%）、及び嘔吐（2%）であった。

[表 1.6.2-33]及び[表 1.6.2-34]に、KEYNOTE-859試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-33　有害事象
KEYTRUDA の投与を受けた患者で発現割合 20%以上
（KEYNOTE-859 試験）

有害事象	KEYTRUDA 200 mg 3 週間間隔投与と FP 又は CAPOX との併用（785 例）		プラセボと FP 又は CAPOX との併用（787 例）	
	All Grades* (%)	Grade 3-4 (%)	All Grades* (%)	Grade 3-4 (%)
神経系障害				
末梢性ニューロパチー†	47	5	48	6
胃腸障害				
悪心	46	3.7	46	4.4
下痢	36	6	32	5
嘔吐	34	5	27	5
腹痛‡	26	2.8	24	2.9
便秘	22	0.5	21	0.8
一般・全身障害および投与部位の状態				
疲労§	40	8	39	9
代謝および栄養障害				
食欲減退	29	3.3	29	2.5
皮膚および皮下組織障害				
手掌・足底発赤知覚不全症候群	25	3.1	22	1.8
臨床検査				
体重減少	20	2.8	19	2.7

*　Grade 分類は NCI CTCAE v4.03 に基づく。
†　異常感覚、知覚過敏、感覚鈍麻、神経痛、末梢性ニューロパチー†、錯感覚、末梢性感覚ニューロパチー、末梢性運動ニューロパチー、及び多発ニューロパチーを含む。
‡　腹部不快感、腹痛、下腹部痛、腹部圧痛、上腹部痛、心窩部不快感、及び消化器痛を含む。
§　無力症及び疲労を含む。

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表 1.6.2-34　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた患者で発現割合 20%以上

（KEYNOTE-859 試験）

臨床検査*	KEYTRUDA 200 mg 3 週間間隔投与と FP 又は CAPOX との併用		プラセボと FP 又は CAPOX との併用	
	All Grades† %	Grade 3-4 %	All Grades† %	Grade 3-4 %
血液				
貧血	65	15	69	13
血小板減少症	64	12	62	10
好中球減少症	63	25	58	20
白血球減少症	59	7	56	6
リンパ球減少症	57	20	51	16
血清生化学				
AST 増加	57	4.7	48	3.6
低アルブミン血症	55	4.1	52	2.9
高血糖	53	6	52	4.6
低カルシウム血症	49	3.6	45	3.3
アルカリホスファターゼ増加	48	6	41	5
低ナトリウム血症	40	13	40	12
ALT 増加	40	4.2	29	2.9
低カリウム血症	35	10	27	9
ビリルビン増加	32	5	30	5
低リン血症	30	10	27	8
低マグネシウム血症	29	0.3	22	0.7
クレアチニン増加	21	3.5	18	1.7
高カリウム血症	20	3.7	18	2.9
INR 増加	20	1.4	22	0

*　各臨床検査値異常の発現割合はベースライン時及び投与後 1 回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA／FP 又は CAPOX 群（210～766 例）、プラセボ／FP 又は CAPOX 群（190～762 例）。

†　Grade 分類は NCI CTCAE v4.03 に基づく。

食道癌

局所進行の切除不能又は転移性の食道癌／食道胃接合部癌の一次治療

KEYNOTE-590試験は、多施設共同、二重盲検、無作為化（1：1）、プラセボ対照の臨床試験であり、外科的切除及び根治的化学放射線療法が不適応の、転移性又は局所進行の食道癌又は食道胃接合部癌（腫瘍の中心が食道胃接合部の上1～5 cm にあるもの）を有する患者を対象に、一次治療として KEYTRUDA をシスプラチン及びフルオロウラシルの化学療法と併用投与した際の安全性を評価した［臨床試験（14.10）参照］。計740例が、シスプラチン最大6コース及びフルオロウラシル最大35コースの両投与との併用により、KEYTRUDA 200 mg（370例）又はプラセボ（370例）の投与を3週間間隔で最大35コース受けた。

投与期間の中央値は、KEYTRUDA 併用投与群では5.7ヵ月（範囲：1日～26ヵ月）、化学療法群では5.1ヵ月（範囲：3日～27ヵ月）であった。

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患者の15%が有害事象によりKEYTRUDAの投与を中止した。高頻度に認められた（1%以上）KEYTRUDAの投与中止に至った有害事象は、肺臓炎（1.6%）、急性腎障害（1.1%）及び肺炎（1.1%）であった。患者の67%が有害事象によりKEYTRUDAを休薬した。高頻度に認められた（2%以上）KEYTRUDAの休薬に至った有害事象は、好中球減少症（19%）、疲労／無力症（8%）、白血球数減少（5%）、肺炎（5%）、食欲減退（4.3%）、貧血（3.2%）、血中クレアチニン増加（3.2%）、口内炎（3.2%）、倦怠感（3.0%）、血小板減少症（3%）、肺臓炎（2.7%）、下痢（2.4%）、嚥下障害（2.2%）及び悪心（2.2%）であった。

[表 1.6.2-35]及び[表 1.6.2-36]に、KEYNOTE-590試験でKEYTRUDAの投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-35　有害事象

KEYTRUDAの投与を受けた食道癌患者で発現割合20%以上（KEYNOTE-590試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与とシスプラチン及びフルオロウラシルとの併用（370例）		プラセボとシスプラチン及びフルオロウラシルとの併用（370例）	
	All Grades* (%)	Grade 3-4† (%)	All Grades* (%)	Grade 3-4† (%)
胃腸障害				
悪心	67	7	63	7
便秘	40	0	40	0
下痢	36	4.1	33	3
嘔吐	34	7	32	5
口内炎	27	6	26	3.8
一般・全身障害および投与部位の状態				
疲労‡	57	12	46	9
代謝および栄養障害				
食欲減退	44	4.1	38	5
臨床検査				
体重減少	24	3.0	24	5

* Grade分類はNCI CTCAE v4.03に基づく。
† 死亡に至った事象の下痢が各群1件報告された。
‡ 無力症及び疲労を含む。

表 1.6.2-36　ベースラインから悪化した臨床検査値異常

KEYTRUDAの投与を受けた食道癌患者で発現割合20%以上（KEYNOTE-590試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与とシスプラチン及びフルオロウラシルとの併用		化学療法（プラセボとシスプラチン及びフルオロウラシルとの併用）	
	All Grades† %	Grade 3-4 %	All Grades† %	Grade 3-4 %
血液				
貧血	83	21	86	24
好中球減少症	74	43	71	41
白血球減少症	72	21	73	17
リンパ球減少症	55	22	53	18
血小板減少症	43	5	46	8

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血清生化学				
高血糖	56	7	55	6
低ナトリウム血症	53	19	54	19
低アルブミン血症	52	2.8	52	2.3
クレアチニン増加	45	2.5	42	2.5
低カルシウム血症	44	3.9	38	2
低リン血症	37	9	31	10
低カリウム血症	30	12	34	15
アルカリホスファターゼ増加	29	1.9	29	1.7
高カリウム血症	28	3.6	27	2.6
AST増加	25	4.4	22	2.8
ALT増加	23	3.6	18	1.7

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA／シスプラチン／フルオロウラシル群：345～365例、プラセボ／シスプラチン／フルオロウラシル群：330～358例。
† Grade分類はNCI CTCAE v4.03に基づく。

既治療の局所進行再発又は転移性の食道癌

KEYNOTE-181試験において、食道癌患者314例のKEYTRUDAの投与期間の中央値は2.1ヵ月（範囲：1日～24.4ヵ月）であった［臨床試験（14.10）参照］。自己免疫疾患を有する患者又は免疫抑制剤治療を必要とする患者は不適格とされた。食道癌患者に発現した有害事象は、KEYTRUDAの単独投与を受けた悪性黒色腫又は非小細胞肺癌の2799例で発現した有害事象と同様であった。

子宮頸癌

FIGO 2014進行期分類のIIIｰIVA期子宮頸癌と化学放射線療法との併用

KEYNOTE-A18試験は、プラセボ対照、無作為化（1：1）、多施設共同、二重盲検の臨床試験であり、FIGO 2014進行期分類のIIIｰIVA期子宮頸癌患者594例を対象に、KEYTRUDAをCRT［シスプラチンと外照射放射線療法（EBRT）との併用後に小線源療法（BT）を施行］と併用した場合の安全性を評価した［臨床試験（14.11）参照］。292例がKEYTRUDAと化学放射線療法との併用療法を受け、302例がプラセボと化学放射線療法との併用療法を受けた。

KEYTRUDAの投与期間の中央値は12.1ヵ月（範囲：1日～27ヵ月）であった。

KEYTRUDAと化学放射線療法との併用療法を受けた患者の1.4%で、死亡に至った有害事象が発現した。このうち、大腸穿孔、尿路性敗血症、敗血症、及び膣出血が各1例（0.3%）であった。

KEYTRUDAと化学放射線療法との併用療法を受けた患者の30%で、重篤な有害事象が発現した。患者の1%以上で認められた重篤な有害事象は、尿路感染（2.7%）、尿路性敗血症（1.4%）、及び敗血症（1%）であった。

患者の7%が有害事象によりKEYTRUDAの投与を中止した。投与中止に至った主な有害事象（1%以上）は、下痢（1%）であった。

患者の43%が有害事象によりKEYTRUDAを休薬した。KEYTRUDAの休薬に至った主な有害事象（2%以上）は、貧血（8%）、COVID-19（6%）、SARS-CoV-2検査陽性（3.1%）、好中球数減少（2.7%）、下痢（2.7%）、尿路感染（2.7%）、及びALT増加（2.4%）であった。

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[表 1.6.2-37]及び[表 1.6.2-38]に KEYNOTE-A18試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-37　有害事象

KEYTRUDA の投与を受けた FIGO 2014 進行期分類の III～IVA 期子宮頸癌患者で発現割合 10%以上（KEYNOTE-A18 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔及び 400 mg 6週間間隔と 化学放射線療法との併用 (292例)		プラセボと 化学放射線療法との併用 (302例)	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
胃腸障害				
悪心	56	0	61	2.3
下痢	50	3.8	50	4.3
嘔吐	33	1	34	1.7
便秘	18	0	18	0.7
腹痛	12	0.7	12	1.7
感染症および寄生虫症				
尿路感染†	32	4.1	31	4.6
一般・全身障害および投与部位の状態				
疲労‡	26	1	27	1.3
発熱	12	0.3	13	0
内分泌障害				
甲状腺機能低下症§	20	0.7	5	0
甲状腺機能亢進症	11	0.3	2.6	0
代謝および栄養障害				
食欲減退	17	0.7	17	0.3
臨床検査				
体重減少	17	1.4	18	1
腎および尿路障害				
排尿困難	11	0.3	12	0
皮膚および皮下組織障害				
発疹¶	11	0.7	7	0.3
生殖系				
骨盤痛	10	1	13	1.3

* Grade 分類は NCI CTCAE v5.0に基づく。
† 尿路感染、シュードモナス性尿路感染、急性腎盂腎炎、膀胱炎、及び大腸菌性尿路感染を含む。
‡ 疲労及び無力症を含む。
§ 甲状腺機能低下症、自己免疫性甲状腺機能低下症を含む。
¶ 多形紅斑、皮膚炎、薬疹、湿疹、発疹、皮膚剥脱、水疱性皮膚炎、斑状丘疹状皮疹、扁平苔癬、異汗性湿疹、ざ瘡様皮膚炎を含む。

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表 1.6.2-38　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた FIGO 2014 進行期分類の III～IVA 期子宮頸癌患者で
発現割合 20%以上（KEYNOTE-A18 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔及び 400 mg 6週間間隔と 化学放射線療法との併用		プラセボと 化学放射線療法との併用	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
血液				
リンパ球減少症	99	96	99	92
白血球減少症	96	46	94	49
貧血	88	31	81	25
好中球減少症	75	32	74	33
血小板減少症	65	8	61	6
血清生化学				
低マグネシウム血症	59	4.2	63	3.4
低ナトリウム血症	54	3.8	47	4
AST 増加	45	1	39	1.7
ALT 増加	44	2.1	44	1
低カルシウム血症	43	4.8	40	4.3
低カリウム血症	42	14	38	10
クレアチニン増加	41	6	43	6
低アルブミン血症	37	0.7	35	1.7
アルカリホスファターゼ増加	34	0.3	33	0.3

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA と化学放射線療法併用群：286～291例及びプラセボと化学放射線療法併用群：298～300例。
† Grade 分類は NCI CTCAE v5.0に基づく。

持続、再発又は転移性子宮頸癌

KEYNOTE-826試験は、多施設共同、二重盲検、無作為化（1：1）、プラセボ対照の臨床試験であり、化学療法未投与（放射線感作薬として同時使用した場合を除く）の持続、再発、又は一次治療の転移性子宮頸癌患者を対象に、KEYTRUDA とベバシズマブ併用又は非併用でのパクリタキセル／シスプラチン又はパクリタキセル／カルボプラチンとの併用投与をした際の安全性を評価した［臨床試験（14.11）参照］。計616例が、PD-L1発現の有無によらず、KEYTRUDA 200 mg 3週間間隔投与とベバシズマブ併用又は非併用での化学療法との併用投与（307例）又はプラセボ3週間間隔投与とベバシズマブ併用又は非併用での化学療法との併用投与（309例）を受けた。

KEYTRUDA の投与期間の中央値は、9.9ヵ月（範囲：1日～26ヵ月）であった。

KEYTRUDA とベバシズマブ併用又は非併用での化学療法との併用投与を受けた患者の4.6%で、死亡に至った有害事象が発現した。その内訳は、出血が3例、敗血症が2例、原因不明の死亡が2例、急性心筋梗塞、自己免疫性脳炎、心停止、脳血管発作、周術期肺塞栓症を伴う大腿骨骨折、腸管穿孔及び骨盤内感染が各1例であった。

KEYTRUDA とベバシズマブ併用又は非併用での化学療法との併用投与を受けた患者の50%で、

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重篤な有害事象が発現した。3%以上の患者に報告された重篤な有害事象は、発熱性好中球減少症（6.8%）、尿路感染（5.2%）、貧血（4.6%）、急性腎障害（3.3%）及び敗血症（3.3%）であった。

患者の15%が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた（1%以上）KEYTRUDA の投与中止に至った有害事象は、大腸炎（1%）であった。

66%の患者が有害事象により KEYTRUDA を休薬した。高頻度に認められた（2%以上）KEYTRUDA の休薬に至った有害事象又は臨床検査値異常は、血小板減少症（15%）、好中球減少症（14%）、貧血（11%）、ALT 増加（6%）、白血球減少症（5%）、疲労／無力症（4.2%）、尿路感染（3.6%）、AST 増加（3.3%）、発熱（3.3%）、下痢（2.6%）、急性腎障害（2.6%）、血中クレアチニン増加（2.6%）、大腸炎（2.3%）、食欲減退（2%）及び咳嗽（2%）であった。

KEYTRUDA、化学療法及びベバシズマブ投与群（196例）で、高頻度に認められた（20%以上）有害事象は、末梢性ニューロパチー（62%）、脱毛症（58%）、貧血（55%）、疲労／無力症（53%）、悪心（41%）、好中球減少症（41%）、下痢（39%）、高血圧（35%）、血小板減少症（35%）、便秘（31%）、関節痛（31%）、嘔吐（30%）、尿路感染（27%）、発疹（26%）、白血球減少症（24%）、甲状腺機能低下症（22%）及び食欲減退（21%）であった。

[表 1.6.2-39]及び[表 1.6.2-40]に、KEYNOTE-826試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-39　有害事象

KEYTRUDA の投与を受けた子宮頸癌患者で発現割合 20%以上（KEYNOTE-826 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔 ベバシズマブ併用又は非併用での化学療法併用* （307例）		プラセボ ベバシズマブ併用又は非併用での化学療法併用* （309例）	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
神経系障害				
末梢性ニューロパチー‡	58	4.2	57	6
皮膚および皮下組織障害				
脱毛症	56	0	58	0
発疹§	22	3.6	15	0.3
一般・全身障害および投与部位の状態				
疲労¶	47	7	46	6
胃腸障害				
悪心	40	2	44	1.6
下痢	36	2	30	2.6
便秘	28	0.3	33	1
嘔吐	26	2.6	27	1.9
筋骨格系および結合組織障害				
関節痛	27	0.7	26	1.3
血管障害				
高血圧	24	9	23	11
感染症および寄生虫症				
尿路感染	24	9	26	8
* 化学療法（パクリタキセル／シスプラチンの併用、又はパクリタキセル／カルボプラチンの併用）				

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† Grade 分類は NCI CTCAE v4.0に基づく。
‡ 末梢性ニューロパチー、末梢性感覚ニューロパチー、末梢性運動ニューロパチー、末梢性感覚運動ニューロパチー及び錯感覚を含む。
§ 発疹、斑状丘疹状皮疹、紅斑性皮疹、斑状皮疹、丘疹性皮疹、そう痒性皮疹及び膿疱性皮疹を含む。
¶ 疲労及び無力症を含む。

表 1.6.2-40　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた子宮頸癌患者で発現割合 20%以上
（KEYNOTE-826 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔 ベバシズマブ併用又は非併用での化学療法併用† （307例）		プラセボ ベバシズマブ併用又は非併用での化学療法併用† （309例）	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades‡ (%)	Grades 3-4 (%)
血液				
貧血	80	35	77	33
白血球減少症	76	27	69	19
好中球減少症	66	39	58	31
リンパ球減少症	61	33	56	33
血小板減少症	57	19	53	15
血清生化学				
高血糖	51	4.7	46	2.3
低アルブミン血症	46	1.3	38	5
低ナトリウム血症	40	14	38	11
ALT 増加	40	7	38	6
AST 増加	40	6	36	3.0
アルカリホスファターゼ増加	38	3.4	40	2.3
低カルシウム血症	37	4.0	31	5
クレアチニン増加	34	5	32	6
低カリウム血症	29	7	26	7
高カリウム血症	23	3.7	27	4.7
高カルシウム血症	21	1.0	20	1.3

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA／化学療法併用群：297～301例、プラセボ／化学療法併用群：299～302例。
† 化学療法（パクリタキセル／シスプラチンの併用、又はパクリタキセル／カルボプラチンの併用）。
‡ Grade 分類は NCI CTCAE v4.0に基づく。

既治療の再発又は転移性子宮頸癌

KEYNOTE-158試験のコホート E では、子宮頸癌患者98例の KEYTRUDA の投与期間の中央値は2.9ヵ月（範囲：1日～22.1ヵ月）であった［臨床試験（14.11）参照］。自己免疫疾患を有する患者又は免疫抑制剤治療を必要とする患者は不適格とされた。

患者の8%が有害事象により KEYTRUDA の投与を中止した。患者の39%が重篤な有害事象を発現した。高頻度に認められた重篤な有害事象は、貧血（7%）、瘻孔（4.1%）、出血（4.1%）及び感染［(4.1%）尿路感染は除く］であった。[表 1.6.2-41]及び[表 1.6.2-42]に KEYNOTE-158試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

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表 1.6.2-41　有害事象

KEYTRUDA の投与を受けた子宮頸癌患者で発現割合 10%以上（KEYNOTE-158 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（98例）	
	All Grades* (%)	Grade 3-4 (%)
一般・全身障害および投与部位の状態		
疲労†	43	5
疼痛‡	22	2.0
発熱	19	1.0
末梢性浮腫§	15	2.0
筋骨格系および結合組織障害		
筋骨格痛¶	27	5
胃腸障害		
下痢#	23	2.0
腹痛 Þ	22	3.1
悪心	19	0
嘔吐	19	1.0
便秘	14	0
代謝および栄養障害		
食欲減退	21	0
血管障害		
出血 ß	19	5
感染症および寄生虫症		
尿路感染 à	18	6
感染（尿路感染以外） è	16	4.1
皮膚および皮下組織障害		
発疹 ð	17	2.0
内分泌障害		
甲状腺機能低下症	11	0
神経系障害		
頭痛	11	2.0
呼吸器、胸郭および縦隔障害		
呼吸困難	10	1.0

* Grade 分類は NCI CTCAE v4.0に基づく。
† 無力症、疲労、嗜眠及び倦怠感を含む。
‡ 乳房痛、癌疼痛、異常感覚、排尿困難、耳痛、歯肉痛、肛径部痛、リンパ節痛、口腔咽頭痛、疼痛、皮膚疼痛、骨盤痛、神経根痛、ストーマ部疼痛及び歯痛を含む。
§ 末梢性浮腫及び末梢腫脹を含む。
¶ 関節痛、背部痛、筋骨格系胸痛、筋骨格痛、筋肉痛、筋炎、頚部痛、非心臓性胸痛及び四肢痛を含む。
# 大腸炎、下痢及び胃腸炎を含む。
Þ 腹部不快感、腹部膨満、腹痛、下腹部痛及び上腹部痛を含む。
ß 鼻出血、血尿、喀血、不正子宮出血、直腸出血、子宮出血及び腟出血を含む。
à 細菌性腎盂腎炎、急性腎盂腎炎、尿路感染、細菌性尿路感染、シュードモナス性尿路感染及び尿路性敗血症を含む。
è 蜂巣炎、クロストリジウム・ディフィシレ感染、医療機器関連感染、蓄膿、丹毒、ヘルペスウイルス感染、感染性新生物、感染、インフルエンザ、下気道うっ血、肺感染、口腔カンジダ症、口腔真菌感染、骨髄炎、シュードモナス感染、気道感染、歯膿瘍、上気道感染、子宮膿瘍及び外陰部腟カンジダ症を含む。
ð 皮膚炎、薬疹、湿疹、紅斑、手掌・足底発赤知覚不全症候群、発疹、全身性皮疹及び斑状丘疹状皮疹を含む。

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表 1.6.2-42　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた子宮頸癌患者で発現割合 20%以上
（KEYNOTE-158 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与	
	All Grades† (%)	Grade 3-4 (%)
血液		
貧血	54	24
リンパ球減少症	47	9
血清生化学		
低アルブミン血症	44	5
アルカリホスファターゼ増加	42	2.6
低ナトリウム血症	38	13
高血糖	38	1.3
AST 増加	34	3.9
クレアチニン増加	32	5
低カルシウム血症	27	0
ALT 増加	21	3.9
低カリウム血症	20	6

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は KEYTRUDA 群：76～79例。
† Grade 分類は NCI CTCAE v4.0に基づく。

10%以上に認められたその他の臨床検査値異常は、低リン酸血症（All Grades：19%、Grade 3-4：6%）、INR 増加（All Grades：19%、Grade 3-4：0%）、高カルシウム血症（All Grades：14%、Grade 3-4：2.6%）、血小板数減少（All Grades：14%、Grade 3-4：1.3%）、活性化部分トロンボプラスチン時間延長（All Grades：14%、Grade 3-4：0%）、低血糖（All Grades：13%、Grade 3-4：1.3%）、白血球数減少（All Grades：13%、Grade 3-4：2.6%）及び高カリウム血症（All Grades：13%、Grade 3-4：1.3%）であった。

肝細胞癌

既治療の肝細胞癌

KEYNOTE-394試験は、多施設共同、二重盲検、無作為化、プラセボ対照の臨床試験であり、既治療の肝細胞癌患者を対象に、KEYTRUDA の安全性を評価した。患者は無作為割付けされ（2：1）、KEYTRUDA 200 mg（299例）又はプラセボ（153例）の静脈内投与を3週間間隔で最大35コース受けた［臨床試験（14.12）参照］。

投与期間の中央値は、KEYTRUDA 群では3.3ヵ月（範囲：1日～27.3ヵ月）、プラセボ群では2.2ヵ月（範囲：1日～15.5ヵ月）であった。患者の13%が有害事象により KEYTRUDA の投与を中止した。KEYTRUDA の投与中止に至った主な有害事象は、腹水（2.3%）であった。患者の26%が有害事象により KEYTRUDA を休薬した。KEYTRUDA の休薬に至った主な有害事象又は臨床検査値異常（2%以上）は、血中ビリルビン増加（9%）、AST 増加（5%）、及び ALT 増加（2%）であった。

[表 1.6.2-43]及び[表 1.6.2-44]に KEYNOTE-394試験で KEYTRUDA の投与を受けた患者の有害

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事象及び臨床検査値異常を示す。

表 1.6.2-43　有害事象

KEYTRUDA の投与を受けた肝細胞癌患者で発現割合 10%以上（KEYNOTE-394 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔（299例）		プラセボ（153例）	
	All Grades* (%)	Grades 3-5 (%)	All Grades* (%)	Grades 3-5 (%)
一般・全身障害および投与部位の状態				
発熱	18	0.7	14	0
皮膚および皮下組織障害				
発疹†	18	0.7	7	0
そう痒症	12	0	4	0
胃腸障害				
下痢	16	1.7	9	0
代謝および栄養障害				
食欲減退	15	0.3	9	0
感染症および寄生虫症				
上気道感染	11	1.0	7	0.7
呼吸器、胸郭および縦隔障害				
咳嗽	11	0	9	0
内分泌障害				
甲状腺機能低下症	10	0	7	0

* Grade 分類は NCI CTCAE v4.03に基づく。
† 皮膚炎、アレルギー性皮膚炎、水疱性皮膚炎、発疹、紅斑性皮疹、斑状丘疹状皮疹、膿疱性皮疹、及び水疱を含む。

表 1.6.2-44　ベースラインから悪化した臨床検査値異常

KEYTRUDA の投与を受けた肝細胞癌患者で発現割合 20%以上（KEYNOTE-394 試験）

臨床検査*	KEYTRUDA		Placebo	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
血清生化学				
AST 増加	54	14	44	12
ビリルビン増加	47	11	36	7
ALT 増加	47	7	32	4.6
γ－グルタミルトランスフェラーゼ（GGT）増加	40	20	39	15
低アルブミン血症	40	0.7	20	0.7
アルカリホスファターゼ増加	39	4.1	34	4
高血糖	36	3.3	26	1.4
低ナトリウム血症	36	11	28	5
低リン血症	30	6	17	4
低カルシウム血症	24	1.4	15	0.7
血液				
リンパ球減少症	44	11	34	4.6
貧血	36	7	30	3.3
血小板数減少	32	4.7	29	2
白血球減少症	30	1.3	21	0.7
好中球減少症	25	4.4	21	2

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA 群：223～297例及びプラセボ群：144～151例。
† Grade 分類は NCI CTCAE v4.03に基づく。

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胆道癌

KEYNOTE-966試験は、多施設共同、二重盲検、無作為化、プラセボ対照の臨床試験であり、進行した病態に対してこれまでに全身療法を受けていない局所進行の切除不能又は転移性の胆道癌患者を対象に、KEYTRUDA をゲムシタビン及びシスプラチンと併用投与した際の安全性を評価した［臨床試験（14.13）参照］。計1063例が、KEYTRUDA 200 mg とゲムシタビン及びシスプラチンの化学療法（529例）又はプラセボとゲムシタビン及びシスプラチンの化学療法（534例）のいずれかの投与を3週間間隔で受けた。

KEYTRUDA の投与期間の中央値は、6ヵ月（範囲：1日～28ヵ月）であった。

患者の15%が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた（1%以上）KEYTRUDA の投与中止に至った有害事象は、肺臓炎（1.3%）であった。

患者の55%が有害事象により KEYTRUDA を休薬した。高頻度に認められた（2%以上）KEYTRUDA の休薬に至った有害事象又は臨床検査値異常は、好中球数減少（18%）、血小板数減少（10%）、貧血（6%）、白血球数減少（4%）、発熱（3.8%）、疲労（3.0%）、胆管炎（2.8%）、ALT 増加（2.6%）、AST 増加（2.5%）及び胆道閉塞（2.3%）であった。

KEYTRUDA 及び化学療法群とプラセボ及び化学療法群を比較したところ、KEYTRUDA の投与を受けた患者とプラセボの投与を受けた患者で発現割合に5%以上の差が認められた有害事象は、発熱（26% vs 20%）、発疹（21% vs 13%）、そう痒症（15% vs 10%）及び甲状腺機能低下症（9% vs 2.6%）であった。Grade 3-4の有害事象の発現割合に臨床的に意味のある群間差は認められなかった。

KEYTRUDA 及び化学療法の投与を受けた患者とプラセボ及び化学療法の投与を受けた患者で発現割合に5%以上の差が認められた臨床検査値異常は、リンパ球減少（69% vs 61%）であった。Grade 3-4の臨床検査値異常の発現割合に臨床的に意味のある群間差は認められなかった。

メルケル細胞癌

KEYNOTE-017試験及び KEYNOTE-913試験におけるメルケル細胞癌患者（105例）の KEYTRUDA の投与期間の中央値は6.3ヵ月（範囲：1日～28ヵ月）であった［臨床試験（14.14）参照］。自己免疫疾患を有する患者又は免疫抑制剤治療を必要とする患者は不適格とされた。メルケル細胞癌患者に発現した有害事象は、KEYTRUDA の単独投与を受けた悪性黒色腫又は非小細胞肺癌の2799例で発現した有害事象と同様であった。発現割合の高い臨床検査値異常（Grade 3-4）は、リパーゼ増加（17%）であった。

腎細胞癌

アキシチニブとの併用による進行性腎細胞癌の一次治療（KEYNOTE-426試験）

KEYNOTE-426試験では、アキシチニブと併用投与した場合の安全性を評価した［臨床試験

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（14.15）参照]。全身性副腎皮質ホルモン剤若しくはその他の免疫抑制剤治療を必要とする医学的状態の患者、又は1型糖尿病、尋常性白斑、シェーグレン症候群及びホルモン補充療法で安定している甲状腺機能低下症以外の重度の自己免疫疾患の既往を有する患者は不適格とされた。患者はKEYTRUDA 200 mg の3週間間隔の点滴静注及びアキシチニブ5 mg の1日2回の経口投与、又はスニチニブ50 mg を1日1回4週間投与後2週間休薬の、いずれかの治療を受けた。KEYTRUDA とアキシチニブの併用療法を受けた期間の中央値は10.4ヵ月（範囲：1日～21.2ヵ月）であった。

試験集団の背景因子は、年齢の中央値が62歳（範囲：30～89歳）であり、65歳以上の割合は40%、男性が71%、白人が80%、Karnofsky Performance Status（KPS）が90～100の患者が80%、KPS が70～80の患者が20%であった。

KEYTRUDA とアキシチニブの併用投与を受けた患者の3.3%で、死亡に至った有害事象が発現した。その内訳は、心停止が3例、肺塞栓症が2例、心不全、原因不明の死亡、重症筋無力症、心筋炎、フルニエ壊疽、形質細胞性骨髄腫、胸水、肺臓炎及び呼吸不全が各1例であった。

KEYTRUDA とアキシチニブの併用投与を受けた患者の40%で、重篤な有害事象が発現した。1%以上の患者に報告された重篤な有害事象は、肝毒性（7%）、下痢（4.2%）、急性腎障害（2.3%）、脱水（1%）及び肺臓炎（1%）であった。

31%の患者で KEYTRUDA 又はアキシチニブのいずれかの投与の中止に至った有害事象が発現した。13%が KEYTRUDA のみ、13%がアキシチニブのみ、8%が両剤の薬剤の投与中止となった。KEYTRUDA、アキシチニブ又は両剤の投与中止に至った、発現割合が高い（1%超）有害事象は、肝毒性（13%）、下痢／大腸炎（1.9%）、急性腎障害（1.6%）及び脳血管発作（1.2%）であった。

KEYTRUDA とアキシチニブの併用投与を受けた患者の76%で、Infusion-related reactions により KEYTRUDA の投与を一時的に中断した場合を除き、休薬又は減量に至った有害事象が発現した。50%の患者で、KEYTRUDA を休薬した。64%の患者でアキシチニブを休薬し、22%の患者でアキシチニブを減量した。KEYTRUDA の休薬に至った高頻度（10%超）に発現した有害事象は、肝毒性（14%）及び下痢（11%）であり、アキシチニブの休薬又は減量のいずれかに至った高頻度（10%超）に発現した有害事象は、肝毒性（21%）、下痢（19%）及び高血圧（18%）であった。

KEYTRUDA とアキシチニブの併用投与を受けた患者で高頻度（20%以上）に認められた有害事象は、下痢、疲労／無力症、高血圧、甲状腺機能低下症、食欲減退、肝毒性、手掌・足底発赤知覚不全症候群、悪心、口内炎／粘膜の炎症、発声障害、発疹、咳嗽及び便秘であった。

KEYTRUDA とアキシチニブの併用投与を受けた27%の患者で、免疫関連の有害事象のために1日あたりプレドニゾロン換算40 mg 以上の経口投与による治療を受けた。

[表 1.6.2-45]及び[表 1.6.2-46]に KEYNOTE-426試験で KEYTRUDA とアキシチニブの投与を受けた患者の20%以上でみられた有害事象及び臨床検査値異常を示す。

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表 1.6.2-45　有害事象

KEYTRUDA とアキシチニブの併用投与を受けた腎細胞癌患者で発現割合 20%以上

（KEYNOTE-426 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔及びアキシチニブ併用投与（429例）		スニチニブ（425例）	
	All Grades* (%)	Grade 3-4 (%)	All Grades* (%)	Grade 3-4 (%)
胃腸障害				
下痢†	56	11	45	5
悪心	28	0.9	32	0.9
便秘	21	0	15	0.2
一般・全身障害および投与部位の状態				
疲労／無力症	52	5	51	10
血管障害				
高血圧‡	48	24	48	20
肝胆道系障害				
肝毒性§	39	20	25	4.9
内分泌障害				
甲状腺機能低下症	35	0.2	32	0.2
代謝および栄養障害				
食欲減退	30	2.8	29	0.7
皮膚および皮下組織障害				
手掌・足底発赤知覚不全症候群	28	5	40	3.8
口内炎／粘膜の炎症	27	1.6	41	4
発疹¶	25	1.4	21	0.7
呼吸器、胸郭および縦隔障害				
発声障害	25	0.2	3.3	0
咳嗽	21	0.2	14	0.5

* Grade 分類は NCI CTCAE v4.03に基づく。
† 下痢、大腸炎、腸炎、胃腸炎、小腸炎及び出血性腸炎を含む。
‡ 高血圧、血圧上昇、高血圧クリーゼ及び不安定高血圧を含む。
§ ALT 増加、AST 増加、自己免疫性肝炎、血中ビリルビン増加、薬物性肝障害、肝酵素上昇、肝機能異常、肝炎、劇症肝炎、肝細胞損傷、肝毒性、高ビリルビン血症、免疫性肝炎、肝機能検査値上昇、肝損傷及びトランスアミナーゼ上昇を含む。
¶ 発疹、蝶形皮疹、皮膚炎、ざ瘡様皮膚炎、アトピー性皮膚炎、水疱性皮膚炎、接触皮膚炎、剥脱性発疹、性器発疹、紅斑性皮疹、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、脂漏性皮膚炎、皮膚変色、皮膚剥脱及び会陰発疹を含む。

表 1.6.2-46　ベースラインから悪化した臨床検査値異常

KEYTRUDA とアキシチニブの併用投与を受けた腎細胞癌患者で発現割合 20%以上

（KEYNOTE-426 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔及びアキシチニブ併用投与		スニチニブ	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
血清生化学				
高血糖	62	9	54	3.2
ALT 増加	60	20	44	5
AST 増加	57	13	56	5
クレアチニン増加	43	4.3	40	2.4
低ナトリウム血症	35	8	29	8
高カリウム血症	34	6	22	1.7
低アルブミン血症	32	0.5	34	1.7

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高カルシウム血症	27	0.7	15	1.9
低リン酸血症	26	6	49	17
アルカリホスファターゼ増加	26	1.7	30	2.7
低カルシウム血症‡	22	0.2	29	0.7
血中ビリルビン増加	22	2.1	21	1.9
活性化部分トロンボプラスチン時間延長§	22	1.2	14	0
血液				
リンパ球減少症	33	11	46	8
貧血	29	2.1	65	8
血小板減少症	27	1.4	78	14

*各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA／アキシチニブ群：342～425例、スニチニブ群：345～422例。
†Grade 分類は NCI CTCAE v4.03に基づく。
‡ アルブミン補正済み。
§ Grade 3の活性化部分トロンボプラスチン時間延長を伴う2例が肝毒性の有害事象も有していた。

レンバチニブとの併用による進行性腎細胞癌の一次治療（KEYNOTE-581試験）

KEYNOTE-581試験で KEYTRUDA の安全性を評価した［臨床試験（14.15）参照］。患者はKEYTRUDA 200 mg の3週間間隔の点滴静注及びレンバチニブ20 mg の1日1回経口投与（352例）、レンバチニブ18 mg の1日1回経口投与及びエベロリムス5 mg の1日1回経口投与（355例）、又はスニチニブ50 mg を1日1回4週間経口投与後2週間休薬（340例）のいずれかの治療を受けた。KEYTRUDA とレンバチニブの併用療法を受けた期間の中央値は17ヵ月（範囲：0.1～39ヵ月）であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の4.3%で、死亡に至った有害事象が発現した。その内訳は、心肺停止（0.9%）、敗血症（0.9%）、不整脈、自己免疫性肝炎、呼吸困難、高血圧クリーゼ、血中クレアチニン増加、多臓器機能不全症候群、筋無力症候群、心筋炎、腎炎、肺臓炎、動脈瘤破裂及びくも膜下出血（各0.3%）であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の51%で、重篤な有害事象が発現した。2%以上の患者に報告された重篤な有害事象は、出血関連事象（5%）、下痢（4%）、高血圧（3%）、心筋梗塞（3%）、肺臓炎（3%）、嘔吐（3%）、急性腎障害（2%）、副腎機能不全（2%）、呼吸困難（2%）及び肺炎（2%）であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の37%に、KEYTRUDA 若しくはレンバチニブのいずれか又は両剤の投与の中止に至った有害事象が発現した。29%が KEYTRUDA のみ、26%がレンバチニブのみ、13%が両剤の投与を中止した。発現割合が高い（2%以上）KEYTRUDA、レンバチニブ又は両剤の投与中止に至った有害事象は、肺臓炎（3%）、心筋梗塞（3%）、肝毒性（3%）、急性腎障害（3%）、発疹（3%）及び下痢（2%）であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の78%で、KEYTRUDA 若しくはレンバチニブのいずれか又は両剤の休薬に至った有害事象が発現した。55%が KEYTRUDA を休薬し、39%が両剤を休薬した。発現割合が高い（3%以上）KEYTRUDA の休薬に至った有害事象は、下痢（10%）、肝毒性（8%）、疲労（7%）、リパーゼ増加（5%）、アミラーゼ増加（4%）、筋骨格痛（3%）、高血

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圧（3%）、発疹（3%）、急性腎障害（3%）及び食欲減退（3%）であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の15%が、免疫関連の有害事象のために1日あたり経口プレドニゾロン換算40 mg 以上のステロイド治療を受けた。

[表 1.6.2-47]及び[表 1.6.2-48]に KEYNOTE-581試験で KEYTRUDA とレンバチニブの投与を受けた患者の20%以上でみられた有害事象及び臨床検査値異常を示す。

表 1.6.2-47　有害事象
KEYTRUDA とレンバチニブの併用投与を受けた腎細胞癌患者で発現割合 20%以上
（KEYNOTE-581 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔及びレンバチニブ併用投与（352例）		スニチニブ50 mg（340例）	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
一般・全身障害および投与部位の状態				
疲労*	63	9	56	8
胃腸障害				
下痢†	62	10	50	6
口内炎‡	43	2	43	2
悪心	36	3	33	1
腹痛§	27	2	18	1
嘔吐	26	3	20	1
便秘	25	1	19	0
筋骨格系および結合組織障害				
筋骨格障害¶	58	4	41	3
内分泌障害				
甲状腺機能低下症#	57	1	32	0
血管障害				
高血圧 Þ	56	29	43	20
出血関連事象 ß	27	5	26	4
代謝および栄養障害				
食欲減退 à	41	4	31	1
皮膚および皮下組織障害				
発疹 è	37	5	17	1
手掌・足底発赤知覚不全症候群 ð	29	4	38	4
臨床検査				
体重減少	30	8	9	0.3
呼吸器、胸郭および縦隔障害				
発声障害	30	0	4	0
腎および尿路障害				
蛋白尿 ø	30	8	13	3
急性腎障害 ý	21	5	16	2
肝胆道系障害				
肝毒性£	25	9	21	5
神経系障害				
頭痛	23	1	16	1

* 無力症、疲労、嗜眠及び倦怠感を含む。
† 下痢及び胃腸炎を含む。
‡ アフタ性潰瘍、歯肉痛、舌炎、舌痛、口腔内潰瘍形成、粘膜の炎症、口腔内不快感、口腔粘膜水疱形成、口腔内痛、口腔咽頭痛、咽頭の炎症及び口内炎を含む。
§ 腹部不快感、腹痛、腹部硬直、腹部圧痛、心窩部不快感、下腹部痛及び上腹部痛を含む。
¶ 関節痛、関節炎、背部痛、骨痛、乳房痛、筋骨格系胸痛、筋骨格不快感、筋骨格痛、筋骨格硬直、筋肉痛、頚部痛、

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非心臓性胸痛、四肢痛及び顎痛を含む。
甲状腺機能低下症、血中甲状腺刺激ホルモン増加及び続発性甲状腺機能低下症を含む。
Þ 本態性高血圧症、血圧上昇、拡張期血圧上昇、高血圧、高血圧クリーゼ、高血圧性網膜症及び不安定血圧を含む。
ß すべての出血関連用語を含む。いずれかの投与群で1例以上に発現した出血関連事象は、肛門出血、動脈瘤破裂、血性水疱、失血性貧血、尿中血陽性、カテーテル留置部位血腫、脳微小出血、結膜出血、挫傷、血性下痢、播種性血管内凝固、斑状出血、鼻出血、眼出血、胃出血、出血性胃炎、歯肉出血、尿路出血、血胸、吐血、血腫、血便排泄、血尿、喀血、痔出血、内出血発生の増加傾向、注射部位血腫、注射部位出血、腹腔内出血、下部消化管出血、マロリー・ワイス症候群、メレナ、点状出血、直腸出血、腎出血、後腹膜出血、小腸出血、線状出血、皮下血腫、硬膜下血腫、くも膜下出血、血栓性血小板減少性紫斑病、腫瘍出血、外傷性血腫及び上部消化管出血。
à 食欲減退及び早期満腹を含む。
è 性器発疹、注入部位発疹、陰茎発疹、会陰発疹、発疹、紅斑性皮疹、斑状皮疹、斑状丘疹状皮疹、丘疹性皮疹、そう痒性皮疹及び膿疱性皮疹を含む。
ð 手掌紅斑、手掌・足底発赤知覚不全症候群及び足底紅斑を含む。
ø ヘモグロビン尿、ネフローゼ症候群及び蛋白尿を含む。
ý 急性腎障害、高窒素血症、血中クレアチニン増加、腎クレアチニン・クリアランス減少、高クレアチニン血症、腎不全、腎機能障害、乏尿、糸球体濾過率減少及び中毒性腎症を含む。
£ 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、血中ビリルビン増加、薬物性肝障害、肝酵素上昇、肝不全、肝機能異常、肝細胞損傷、肝毒性、高ビリルビン血症、高トランスアミナーゼ血症、免疫性肝炎、肝機能検査値上昇、肝損傷、トランスアミナーゼ上昇及びγ－グルタミルトランスフェラーゼ増加を含む。

KEYTRUDA とレンバチニブの併用投与を受けた患者の20%未満で認められた臨床的に重要な有害事象は、心筋梗塞（3%）及び狭心症（1%）であった。

表 1.6.2-48　　ベースラインから悪化した臨床検査値異常
KEYTRUDA とレンバチニブの併用投与を受けた腎細胞癌患者で発現割合 20%以上（All Grades）
（KEYNOTE-581 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔及びレンバチニブ併用投与		スニチニブ50 mg	
	All Grades %†	Grade 3-4 %†	All Grades %†	Grade 3-4 %†
血清生化学				
高トリグリセリド血症	80	15	71	15
高コレステロール血症	64	5	43	1
リパーゼ増加	61	34	59	28
クレアチニン増加	61	5	61	2
アミラーゼ増加	59	17	41	9
AST 増加	58	7	57	3
高血糖	55	7	48	3
ALT 増加	52	7	49	4
高カリウム血症	44	9	28	6
低血糖	44	2	27	1
低ナトリウム血症	41	12	28	9
アルブミン減少	34	0.3	22	0
アルカリホスファターゼ増加	32	4	32	1
低カルシウム血症	30	2	22	1
低リン酸血症	29	7	50	8
低マグネシウム血症	25	2	15	3
クレアチンホスホキナーゼ増加	24	6	36	5
高マグネシウム血症	23	2	22	3
高カルシウム血症	21	1	11	1
血液				
リンパ球減少症	54	9	66	15
血小板減少症	39	2	73	13

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臨床検査*	KEYTRUDA 200 mg 3週間間隔及びレンバチニブ併用投与		スニチニブ50 mg	
	All Grades %†	Grade 3-4 %†	All Grades %†	Grade 3-4 %†
貧血	38	3	66	8
白血球減少症	34	1	77	8
好中球減少症	31	4	72	16

* ベースラインから少なくとも1グレードの悪化が認められた。
† 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA 及びレンバチニブ群：343～349例、スニチニブ群：329～335例。

Grade 3及び4の ALT 増加又は AST 増加は患者の9%に認められた。Grade 2以上の ALT 増加又は AST 増加は64例（18%）に発現し、そのうち20例（31%）は1日あたり経口プレドニゾロン換算40 mg 以上のステロイド投与を受けた。KEYTRUDA とレンバチニブ両剤の投与を再開した患者（38例）中10例で Grade 2以上の ALT 増加又は AST 増加が再発したが、KEYTRUDA のみの投与を再開した患者（3例）に再発はみられなかった。

腎細胞癌の術後補助療法

KEYNOTE-564試験は、腎細胞癌に対して腎摘出術を行った患者984例に、KEYTRUDA 200 mg を3週間間隔で点滴静注（488例）又はプラセボ（496例）を最長1年間投与した無作為化（1：1）、二重盲検、プラセボ対照の臨床試験であり、KEYTRUDA の単独投与時の安全性を評価した［臨床試験（14.15）参照］。KEYTRUDA の投与期間の中央値は11.1ヵ月（範囲：1日～14.3ヵ月）であった。自己免疫疾患を有する患者又は免疫抑制剤治療を必要とする医学的状態の患者は不適格とされた。

KEYTRUDA の投与を受けた患者の20%で、重篤な有害事象が発現した。1%以上の患者に報告された重篤な有害事象は、急性腎障害、副腎機能不全、肺炎、大腸炎及び糖尿病性ケトアシドーシス（各1%）であった。KEYTRUDA の投与を受けた患者の0.2%で、死亡に至った有害事象が発現し、1例で死亡に至った肺炎が発現した。

患者の21%が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた（1%以上）有害事象は、ALT 増加（1.6%）、大腸炎（1%）及び副腎機能不全（1%）であった。

患者の26%が有害事象により KEYTRUDA を休薬した。高頻度に認められた（1%以上）休薬に至った有害事象は、AST 増加（2.3%）、関節痛（1.6%）、甲状腺機能低下症（1.6%）、下痢（1.4%）、ALT 増加（1.4%）、疲労（1.4%）、発疹、食欲減退及び嘔吐（各1%）であった。[表 1.6.2-49]及び[表 1.6.2-50]に KEYNOTE-564試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

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表 1.6.2-49　有害事象*

KEYTRUDA の投与を受けた腎細胞癌患者で発現割合 10%以上

（KEYNOTE-564 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与（488例）		プラセボ（496例）	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
筋骨格系および結合組織障害				
筋骨格痛‡	41	1.2	36	0.6
一般・全身障害および投与部位の状態				
疲労§	40	1.2	31	0.2
皮膚および皮下組織障害				
発疹¶	30	1.4	15	0.4
そう痒症	23	0.2	13	0
胃腸障害				
下痢#	27	2.7	23	0.2
悪心	16	0.4	10	0
腹痛 Þ	11	0.4	13	0.2
内分泌障害				
甲状腺機能低下症	21	0.2	3.6	0
甲状腺機能亢進症	12	0.2	0.2	0
呼吸器、胸郭および縦隔障害				
咳嗽 ß	17	0	12	0
神経系障害				
頭痛 à	15	0.2	13	0
肝胆道系障害				
肝毒性 è	14	3.7	7	0.6
腎および尿路障害				
急性腎障害 ð	13	1.2	10	0.2

* プラセボ群と同程度又はそれ以上の発現割合であった有害事象を選択した。
† Grade 分類は NCI CTCAE v4.0に基づく。
‡ 関節痛、背部痛、筋肉痛、関節炎、四肢痛、頚部痛、筋骨格痛、筋骨格硬直、脊椎痛、筋骨格系胸痛、骨痛及び筋骨格不快感を含む。
§ 無力症及び疲労を含む。
¶ 発疹、斑状丘疹状皮疹、丘疹性皮疹、皮膚剥脱、扁平苔癬、紅斑性皮疹、湿疹、斑状皮疹、ざ瘡様皮膚炎、皮膚炎、そう痒性皮疹、スティーヴンス・ジョンソン症候群、皮脂欠乏性湿疹及び手掌・足底発赤知覚不全症候群を含む。
# 下痢、大腸炎、腸炎、排便回数増加及び小腸炎を含む。
Þ 腹痛、下腹部痛、上腹部痛、腹部不快感及び消化器痛を含む。
ß 上気道咳症候群、湿性咳嗽及び咳嗽を含む。
à 緊張性頭痛、頭痛、副鼻腔炎に伴う頭痛及び前兆を伴う片頭痛を含む。
è 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、血中ビリルビン増加、薬物性肝障害、肝酵素上昇、肝機能異常、肝細胞損傷、肝毒性、高ビリルビン血症、免疫性肝炎、肝機能検査値上昇、トランスアミナーゼ上昇、γ－グルタミルトランスフェラーゼ増加及び抱合ビリルビン増加を含む。
ð 急性腎障害、血中クレアチニン増加、腎不全、腎機能障害、乏尿、糸球体濾過率減少及び中毒性腎症を含む。

表 1.6.2-50　ベースラインから悪化した臨床検査値異常*

KEYTRUDA の投与を受けた腎細胞癌患者で発現割合 20%以上

（KEYNOTE-564 試験）

臨床検査†	KEYTRUDA 200 mg 3週間間隔投与		プラセボ	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
血清生化学				
ブドウ糖増加	48	8	45	4.5
クレアチニン増加	40	1.1	28	0.2
INR 増加	27	0.9	20	0.8

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低ナトリウム血症	21	3.3	13	1.9
ALT 増加	20	3.8	11	0.2
血液				
貧血	28	0.5	20	0.4

* プラセボ群と同程度又はそれ以上の発現割合であった臨床検査値異常を選択した。
† 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA 群：440～449例、プラセボ群：461～469例。INR 増加については、KEYTRUDA 群：228例、プラセボ群：254例。
‡ Grade 分類は NCI CTCAE v4.03に基づく。

子宮体癌

原発性進行又は再発子宮体癌

KEYTRUDA と化学療法（パクリタキセル及びカルボプラチン）を併用投与した場合の安全性を、進行又は再発子宮体癌患者を対象とした無作為化（1：1）、多施設共同、二重盲検、プラセボ対照試験である KEYNOTE-868試験で評価した［臨床試験（14.16）参照］。計759例の患者に KEYTRUDA 200 mg の3週間間隔投与と化学療法を6サイクル併用投与後に KEYTRUDA 400 mg の6週間間隔投与を最大14サイクル（382例）、又はプラセボと化学療法を6サイクル併用投与後にプラセボを最大14サイクル投与した（377例）。KEYTRUDA の投与期間の中央値は5.6ヵ月（範囲：1日から24.0ヵ月）であった。

重篤な有害事象は、KEYTRUDA と化学療法を併用投与した患者の35%で発現したのに対し、プラセボと化学療法を併用投与した患者の19%で発現した。

KEYTRUDA と化学療法を併用投与した患者の1.6%で死亡に至る有害事象が発現し、内訳は COVID-19（0.5%）及び心停止（0.3%）であった。

患者の14%が有害事象のため KEYTRUDA の投与を中止した。化学療法の減量を要した患者の割合は、KEYTRUDA と化学療法を併用投与した患者では29%であったのに対し、プラセボと化学療法を併用投与した患者では23%であった。両群間で化学療法の中止又は中断における臨床的に意義のある差はなかった。

KEYTRUDA と化学療法を併用投与した患者で発現した有害事象は、発疹（All Grades：33%、Grade 3-4：2.9%）を除き、KEYTRUDA 単独投与又は化学療法単独投与で認められたものと概ね同様であった。

pMMR である又は MSI-High を有さない進行子宮体癌に対する KEYTRUDA とレンバチニブの併用投与による治療

KEYNOTE-775試験は、多施設、非盲検、無作為化（1：1）、実薬対照の臨床試験であり、術前補助療法及び術後補助療法を含めた1種類以上のプラチナ製剤併用化学療法レジメンによる治療を受けた進行性の子宮体癌患者が組み入れられ、レンバチニブと併用投与した場合の安全性を評価した［臨床試験（14.16）参照］。pMMR である又は MSI-High を有さない子宮体癌患者に KEYTRUDA 200 mg の3週間間隔投与とレンバチニブ20 mg の1日1回経口投与を併用投与（342例）、又はドキソルビシン若しくはパクリタキセルを投与した（325例）。

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腫瘍が pMMR である又は MSI-High を有さない状態の患者の治験薬の投与期間の中央値は7.2ヵ月（範囲：1日～26.8ヵ月）、KEYTRUDA の投与期間の中央値は6.8ヵ月（範囲：1日～25.8ヵ月）であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の4.7%で、死亡に至った有害事象が発現した。その内訳は、肺炎が2例、急性腎障害、急性心筋梗塞、大腸炎、食欲減退、腸管穿孔、下部消化管出血、悪性消化管閉塞、多臓器機能不全症候群、骨髄異形成症候群、肺塞栓症及び右室機能不全が各1例であった。

KEYTRUDA とレンバチニブの併用投与を受けた患者の50%で、重篤な有害事象が発現した。3%以上の患者に報告された重篤な有害事象は、高血圧（4.4%）及び尿路感染（3.2%）であった。

患者の15%が有害事象により KEYTRUDA の投与を中止した。高頻度に認められた（1%以上）投与中止に至った有害事象は、ALT 増加（1.2%）であった。

患者の48%が有害事象により KEYTRUDA を休薬した。高頻度に認められた（3%以上）休薬に至った有害事象は、下痢（8%）、ALT 増加（4.4%）、AST 増加（3.8%）及び高血圧（3.5%）であった。

[表 1.6.2-51]及び[表 1.6.2-52]に KEYNOTE-775試験で KEYTRUDA とレンバチニブの併用投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-51　有害事象
KEYTRUDA とレンバチニブの併用投与を受けた子宮体癌患者で発現割合 20%以上
（KEYNOTE-775 試験）

有害事象	子宮体癌（pMMR である又は MSI-High を有さない）			
	KEYTRUDA 200 mg 3週間間隔及びレンバチニブ併用投与（342例）		ドキソルビシン又はパクリタキセル（325例）	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
内分泌障害				
甲状腺機能低下症†	67	0.9	0.9	0
血管障害				
高血圧‡	67	39	6	2.5
出血関連事象§	25	2.6	15	0.9
一般・全身障害および投与部位の状態				
疲労¶	58	11	54	6
胃腸障害				
下痢#	55	8	20	2.8
悪心	49	2.9	47	1.5
嘔吐	37	2.3	21	2.2
口内炎 Þ	35	2.6	26	1.2
腹痛 ß	34	2.6	21	1.2
便秘	27	0	25	0.6
筋骨格系および結合組織障害				
筋骨格障害 à	53	5	27	0.6

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代謝および栄養障害				
食欲減退[è]	44	7	21	0
臨床検査				
体重減少	34	10	6	0.3
腎および尿路障害				
蛋白尿[ð]	29	6	3.4	0.3
感染症および寄生虫症				
尿路感染[ø]	31	5	13	1.2
神経系障害				
頭痛	26	0.6	9	0.3
呼吸器、胸郭および縦隔障害				
発声障害	22	0	0.6	0
皮膚および皮下組織障害				
手掌・足底発赤知覚不全[ý]	23	2.9	0.9	0
発疹[£]	20	2.3	4.9	0

* Grade 分類は NCI CTCAE v4.03に基づく。
† 甲状腺機能低下症、血中甲状腺刺激ホルモン増加、甲状腺炎及び続発性甲状腺機能低下症を含む。
‡ 高血圧、血圧上昇、二次性高血圧、血圧異常、高血圧性脳症及び血圧変動を含む。
§ 鼻出血、膣出血、血尿、歯肉出血、不正子宮出血、直腸出血、挫傷、血便排泄、脳出血、結膜出血、胃腸出血、喀血、尿路出血、下部消化管出血、口腔内出血、点状出血、子宮出血、肛門出血、血性水疱、眼出血、血腫、頭蓋内出血、出血性卒中、メレナ、ストーマ部出血、上部消化管出血、創傷出血、尿中血陽性、斑状出血、吐血、皮下出血、肝血腫、注射部位内出血、腸出血、喉頭出血、肺出血、硬膜下血腫、臍出血及び血管穿刺部位内出血を含む。
¶ 疲労、無力症、倦怠感及び嗜眠を含む。
# 下痢及び胃腸炎を含む。
Þ 口内炎、粘膜の炎症、口腔咽頭痛、アフタ性潰瘍、口腔内潰瘍形成、口唇炎、口腔粘膜紅斑及び舌潰瘍を含む。
ß 腹痛、上腹部痛、下腹部痛、腹部不快感、消化器痛、腹部圧痛及び心窩部不快感を含む。
à 関節痛、筋肉痛、背部痛、四肢痛、骨痛、頚部痛、筋骨格痛、関節炎、筋骨格系胸痛、筋骨格硬直、非心臓性胸痛及び顎痛を含む。
è 食欲減退及び早期満腹を含む。
ð 蛋白尿、尿中蛋白陽性及びヘモグロビン尿を含む。
ø 尿路感染、膀胱炎及び腎盂腎炎を含む。
ý 手掌・足底発赤知覚不全症候群、手掌紅斑及び足底紅斑を含む。
£ 発疹、斑状丘疹状皮疹、そう痒性皮疹、紅斑性皮疹、斑状皮疹、膿疱性皮疹、丘疹性皮疹、小水疱性皮疹及び適用部位発疹を含む。

表 1.6.2-52　ベースライン*から悪化した臨床検査値異常
KEYTRUDA とレンバチニブの併用投与を受けた子宮体癌患者で
発現割合 20%以上（すべての Grade）又は 3%以上（Grade 3 又は 4）
（KEYNOTE-775 試験）

臨床検査†	子宮体癌（pMMR である又は MSI-High を有さない）			
	KEYTRUDA 200 mg 3週間間隔及びレンバチニブ併用投与		ドキソルビシン又はパクリタキセル	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
血清生化学				
高トリグリセリド血症	70	6	45	1.7
低アルブミン血症	60	2.7	42	1.6
AST 増加	58	9	23	1.6
高血糖	58	8	45	4.4
低マグネシウム血症	53	6	32	3.8
ALT 増加	55	9	21	1.2
高コレステロール血症	53	3.2	23	0.7
低ナトリウム血症	46	15	28	7
アルカリホスファターゼ増加	43	4.7	18	0.9
低カルシウム血症	40	4.7	21	1.9
リパーゼ増加	36	14	13	3.9
クレアチニン増加	35	4.7	18	1.9

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低カリウム血症	34	10	24	5
低リン酸血症	26	8	17	3.2
アミラーゼ増加	25	7	8	1
高カリウム血症	23	2.4	12	1.2
クレアチンキナーゼ増加	19	3.7	7	0
ビリルビン増加	18	3.6	6	1.6
血液				
リンパ球減少症	50	16	65	20
血小板減少症	50	8	30	4.7
貧血	49	8	84	14
白血球減少症	43	3.5	83	43
好中球減少症	31	6	76	58

* ベースラインから少なくとも1グレードの悪化が認められた。
† 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数はKEYTRUDA 及びレンバチニブ群：263～340例、ドキソルビシン又はパクリタキセル群：240～322例。
‡ Grade 分類は NCI CTCAE v4.03に基づく。

MSI-High 又は MMR 欠損を有する進行子宮体癌に対する KEYTRUDA の単独投与による治療

KEYNOTE-158試験に組み入れられ、KEYTRUDA の単独投与を受けた MSI-High を有する又は MMR 欠損を有する子宮体癌患者90例では［臨床試験（14.16）参照］、KEYTRUDA の投与期間の中央値は8.3ヵ月（範囲：1日～26.9ヵ月）であった。子宮体癌患者に発現した有害事象は、KEYTRUDA の単独投与を受けた悪性黒色腫又は NSCLC 患者2799例で発現した有害事象と同様であった。

腫瘍遺伝子変異量高値の癌（TMB-High 癌）

KEYNOTE-158試験では、TMB-High 癌患者105例が組み入れられ、KEYTRUDA を投与した際の安全性を評価した［臨床試験（14.17）参照］。KEYTRUDA 投与期間の中央値は4.9ヵ月（範囲：0.03～35.2ヵ月）であった。TMB-High 癌患者に発現した有害事象は、KEYTRUDA の単独投与を受けた他の固形がん患者で発現した有害事象と同様であった。

皮膚扁平上皮癌（cSCC）

KEYNOTE-629試験において、進行性 cSCC（再発若しくは転移性又は局所進行）患者159例の KEYTRUDA 投与期間の中央値は6.9ヵ月（範囲：1日～28.9ヵ月）であった［臨床試験（14.18）参照］。自己免疫疾患を有する患者又は全身性副腎皮質ホルモン剤若しくはその他の免疫抑制剤による治療を必要とした医学的状態の患者は不適格とされた。再発若しくは転移性の cSCC 又は局所進行の cSCC 患者に発現した有害事象は、KEYTRUDA の単独投与を受けた悪性黒色腫又は非小細胞肺癌の2799例で発現した有害事象と同様であった。発現割合の高い臨床検査値異常（Grade 3-4）は、リンパ球減少症（10%）及びナトリウム減少（10%）であった。

トリプルネガティブ乳癌

高リスク早期トリプルネガティブ乳癌に対する術前補助療法及び術後補助療法

KEYNOTE 522試験は、無作為化（2：1）、多施設共同、二重盲検、プラセボ対照の臨床試験であり、新たに診断された、未治療の高リスク早期トリプルネガティブ乳癌患者を対象に、KEYTRUDA

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を術前補助療法として化学療法（カルボプラチン及びパクリタキセル投与後にドキソルビシン又はエピルビシン及びシクロホスファミドを投与）と併用投与、及び術後補助療法として単独投与した際の安全性を評価した。

合計778例が少なくとも1回、化学療法を併用する術前補助療法及び術後補助療法としてKEYTRUDA の投与を受け、その結果を化学療法を併用する術前補助療法及び術後補助療法としてプラセボの投与を受けた389例と比較した［臨床試験（14.19）］。

KEYTRUDA 200 mg 3週間間隔投与の投与期間の中央値は、13.3ヵ月（範囲：1日～21.9ヵ月）であった。

KEYTRUDA の投与を受けた患者の0.9%で、死亡に至った有害事象が発現した。その内訳は、副腎クリーゼ、自己免疫性脳炎、肝炎、肺炎、肺臓炎、肺塞栓症、及び多臓器機能不全症候群と心筋梗塞を伴う敗血症（各1例）であった。

KEYTRUDA の投与を受けた患者の44%で、重篤な有害事象が発現した。KEYTRUDA の投与を受けた患者の2%以上に報告された重篤な有害事象は、発熱性好中球減少症（15%）、発熱（3.7%）、貧血（2.6%）及び好中球減少症（2.2%）であった。

患者の20%が有害事象により KEYTRUDA の投与を中止した。投与中止に至った有害事象のうち高頻度に認められた（1%以上）事象は、ALT 増加（2.7%）、AST 増加（1.5%）及び発疹（1%）であった。患者の57%が有害事象により KEYTRUDA を休薬した。高頻度に認められた（2%以上）KEYTRUDA の休薬に至った有害事象は、好中球減少症（26%）、血小板減少症（6%）、ALT 増加（6%）、AST 増加（3.7%）、貧血（3.5%）、発疹（3.2%）、発熱性好中球減少症（2.8%）、白血球減少症（2.8%）、上気道感染（2.6%）、発熱（2.2%）及び疲労（2.1%）であった。

[表 1.6.2-53]及び[表 1.6.2-54]に、KEYNOTE 522試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常をそれぞれ示す。

表 1.6.2-53　　有害事象

KEYTRUDA の投与を受けた患者で発現割合 20%以上（KEYNOTE-522 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与と化学療法の併用*／KEYTRUDA（778例）		プラセボ 化学療法の併用*／プラセボ（389例）	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
一般・全身障害および投与部位の状態				
疲労‡	70	8	66	3.9
発熱	28	1.3	19	0.3
胃腸障害				
悪心	67	3.7	66	1.8
便秘	42	0	39	0.3
下痢	41	3.2	34	1.8
口内炎§	34	2.7	29	1
嘔吐	31	2.7	28	1.5

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腹痛¶	24	0.5	23	0.8
皮膚および皮下組織障害				
脱毛症	61	0	58	0
発疹#	52	5	41	0.5
神経系障害				
末梢性ニューロパチーÞ	41	3.3	42	2.3
頭痛	30	0.5	29	1
筋骨格系および結合組織障害				
関節痛	29	0.5	31	0.3
筋肉痛	20	0.5	19	0
呼吸器、胸郭および縦隔障害				
咳嗽ß	26	0.1	24	0
代謝および栄養障害				
食欲減退	23	0.9	17	0.3
精神障害				
不眠症	21	0.5	19	0

* 化学療法：カルボプラチン及びパクリタキセル投与後にドキソルビシン又はエピルビシン及びシクロホスファミド
† Grade 分類は NCI CTCAE v4.0に基づく。
‡ 無力症及び疲労を含む。
§ アフタ性潰瘍、口唇炎、口唇痛、口唇潰瘍、口腔内潰瘍形成、粘膜の炎症、口腔粘膜疹、口腔内痛、口内炎、舌水疱形成及び舌潰瘍を含む。
¶ 腹部不快感、腹痛、下腹部痛、上腹部痛及び腹部圧痛を含む。
# 皮膚炎、ざ瘡様皮膚炎、アレルギー性皮膚炎、水疱性皮膚炎、全身性剥脱性皮膚炎、薬疹、湿疹、切開部位発疹、注射部位発疹、発疹、紅斑性皮疹、毛孔性皮疹、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、膿疱性皮疹、風疹状皮疹、皮膚剥脱、皮膚毒性、中毒性皮疹、蕁麻疹、血管炎性皮疹及びウイルス性発疹を含む。
Þ 末梢性ニューロパチー、末梢性運動ニューロパチー、末梢性感覚運動ニューロパチー及び末梢性感覚ニューロパチーを含む。
ß 咳嗽、湿性咳嗽及び上気道咳症候群を含む。

表 1.6.2-54　　ベースラインから悪化した臨床検査値異常
KEYTRUDA の投与を受けた患者で発現割合 20%以上（KEYNOTE-522 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与と化学療法の併用†／KEYTRUDA		プラセボ 化学療法の併用†／プラセボ	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
血液				
貧血	97	22	96	19
白血球減少症	93	41	91	32
好中球減少症	88	62	89	62
リンパ球減少症	80	28	74	22
血小板減少症	58	11	57	9
血清生化学				
ALT 増加	71	9	69	4.6
AST 増加	66	6	58	1.8
高血糖	65	5	62	2.8
アルカリホスファターゼ増加	41	1	37	0.8
低ナトリウム血症	38	9	28	6
低アルブミン血症	36	1.2	30	1.5
低カルシウム血症	32	3.2	29	4.4
低カリウム血症	32	6	24	2.8
低リン酸血症	23	6	18	4.5
高カルシウム血症	21	3	24	3.4

* 各臨床検査値異常の発現割合はベースライン時及び投与後1回以上の臨床検査を実施した患者数に基づく。患者数は、KEYTRUDA を化学療法と併用投与後に単独投与した群：759～777例、プラセボを化学療法と併用投与後に単独投与した群：378～389例。
† 化学療法：カルボプラチン及びパクリタキセル投与後にドキソルビシン又はエピルビシン及びシクロホスファミド

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† Grade 分類は NCI CTCAE v4.0に基づく。

局所再発性・切除不能又は転移性のトリプルネガティブ乳癌

KEYNOTE-355試験では、KEYTRUDA をパクリタキセル、nab-パクリタキセル又はゲムシタビン及びカルボプラチンと併用投与した際の安全性を評価した。KEYNOTE-355試験は多施設、二重盲検、無作為化（2：1）、プラセボ対照試験であり、局所再発性・切除不能又は転移性トリプルネガティブ乳癌で、転移時に化学療法を受けていない患者を対象とした［臨床試験（14.19）参照］。596例の患者（安全性 run-in から開始した34例を含む）に KEYTRUDA 200 mg の3週間間隔投与とパクリタキセル、nab-パクリタキセル又はゲムシタビン及びカルボプラチンとを併用投与した。

KEYTRUDA の投与期間の中央値は5.7ヵ月（範囲：1日～33.0ヵ月）であった。

KEYTRUDA と化学療法の併用投与を受けた患者の2.5%で死亡に至る有害事象が発現した（心肺停止0.7%及び敗血症性ショック0.3%を含む）。

KEYTRUDA とパクリタキセル、nab-パクリタキセル又はゲムシタビン及びカルボプラチンとの併用投与を受けた患者の30%で重篤な有害事象が発現した。2%以上の患者に発現した重篤な有害事象は、肺炎（2.9%）、貧血（2.2%）及び血小板減少症（2%）であった。

有害事象による投与中止は11%の患者で認められた。投与中止に至る有害事象のうち高頻度に認められた（1%以上）事象は、ALT 増加（2.2%）、AST 増加（1.5%）及び肺臓炎（1.2%）であった。有害事象による休薬は50%の患者で認められた。休薬に至る有害事象のうち高頻度に認められた（2%以上）事象は、好中球減少症（22%）、血小板減少症（14%）、貧血（7%）、ALT 増加（6%）、白血球減少症（5%）、AST 増加（5%）、白血球数減少（3.9%）及び下痢（2%）であった。

[表 1.6.2-55]及び[表 1.6.2-56]に、KEYNOTE-355試験で KEYTRUDA の投与を受けた患者の有害事象及び臨床検査値異常を示す。

表 1.6.2-55　有害事象

KEYTRUDA と化学療法を併用された患者で発現割合 20%以上（KEYNOTE-355 試験）

有害事象	KEYTRUDA 200 mg 3週間間隔投与を化学療法と併用（596例）		プラセボ 3週間間隔投与を化学療法と併用（281例）	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
一般・全身障害および投与部位の状態				
疲労†	48	5	49	4.3
胃腸障害				
悪心	44	1.7	47	1.8
下痢	28	1.8	23	1.8
便秘	28	0.5	27	0.4
嘔吐	26	2.7	22	3.2
皮膚および皮下組織障害				

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脱毛症	34	0.8	35	1.1
発疹‡	26	2	16	0
呼吸器、胸郭および縦隔障害				
咳嗽§	23	0	20	0.4
代謝および栄養障害				
食欲減退	21	0.8	14	0.4
神経系障害				
頭痛¶	20	0.7	23	0.7

* Grade分類はNCI CTCAE v4.03に基づく。
† 疲労及び無力症を含む。
‡ 発疹、斑状丘疹状皮疹、そう痒性皮疹、膿疱性皮疹、斑状皮疹、丘疹性皮疹、蝶形皮疹、紅斑性皮疹及び眼瞼発疹を含む。
§ 咳嗽、湿性咳嗽及び上気道咳症候群を含む。
¶ 頭痛、片頭痛及び緊張性頭痛を含む。

表 1.6.2-56　ベースラインから悪化した臨床検査値異常
KEYTRUDA と化学療法を併用された患者で発現割合 20%以上
（KEYNOTE-355 試験）

臨床検査*	KEYTRUDA 200 mg 3週間間隔投与を化学療法と併用		プラセボ 3週間間隔投与を化学療法と併用	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
血液				
貧血	90	20	85	19
白血球減少症	85	39	86	39
好中球減少症	76	49	77	52
リンパ球減少症	70	26	70	19
血小板減少症	54	19	53	21
血液生化学				
ALT増加	60	11	58	8
AST増加	57	9	55	6
高血糖	52	4.4	51	2.2
低アルブミン血症	37	2.2	32	2.2
アルカリホスファターゼ増加	35	3.9	39	2.2
低カルシウム血症	29	3.3	27	1.8
低ナトリウム血症	28	5	26	6
低リン酸血症	21	7	18	4.8
低カリウム血症	20	4.4	18	4.0

* 各臨床検査値異常の発現割合は、ベースライン時及び治験期間中に1つ以上の臨床検査結果が得られている患者数に基づく：KEYTRUDA +化学療法（566～592例）、プラセボ+化学療法（269～280例）
† Grade分類はNCI CTCAE v4.03に基づく。

6.2　市販後の使用経験

KEYTRUDA の市販承認後の使用において、以下の事象が副作用として報告されている。ただし、母数が特定できない集団から任意に報告された事象であることから、必ずしも発現頻度を確実に推算したり、本剤との因果関係を立証したりできるとは限らない。

肝胆道系障害：硬化性胆管炎

特殊集団への投与

8　特殊集団への投与

8.1　妊娠

リスクの要約

KEYTRUDA の作用機序から、妊婦に投与した場合、胎児に危険を及ぼす可能性がある。胚胎児毒性のリスクを示すヒトにおけるデータは得られていない。動物モデルでは、PD-1/PD-L1シグナル伝達経路は、胎児組織に対する母体の免疫寛容を誘導することにより、妊娠を維持する際に重要である（データ参照）。ヒト免疫グロブリン G4は胎盤を通過することが報告されており、KEYTRUDA は母体から発達中の胎児へ移行する可能性がある。妊娠中に本剤を使用する場合、胎児への潜在的なリスクを患者に伝えること。

米国の一般集団で臨床的に認められた妊娠において推定される主な先天性欠損及び流産の背景リスクは、それぞれ2%～4%及び15%～20%である。

データ

動物データ

生殖及び胎児発達への KEYTRUDA の影響を評価するための動物生殖試験は実施されていないが、PD-1/PD-L1経路の中心的機能は胎児に対する母体の免疫寛容を維持することによる妊娠の維持であり、PD-1経路の生殖に及ぼす影響が文献にて示されている。妊娠中のマウスモデルにおいて、PD-L1シグナル伝達の阻害によって胎児への免疫寛容が無効となり、胎児消失が増加することが示されている。したがって、妊娠中に本剤を投与すると、流産率や死産率の上昇などの潜在的なリスクが生じると考えられる。文献で報告されているとおり、文献中の動物の子孫における PD-1シグナル伝達の阻害に関連した奇形は認められていないが、PD-1ノックアウトマウスにおいて免疫性障害が認められている。本剤の作用機序から、本剤の胎児への曝露は、免疫介在性疾患の発現又は正常な免疫応答の変化といったリスクを増加させる可能性がある。

8.2　授乳

リスクの要約

KEYTRUDA の動物又はヒト乳汁中への移行に関するデータ、及び授乳中の乳児又は乳汁産生への影響に関するデータはない。母体の IgG が母乳中に存在することが知られている。母乳で育てられた乳児の KEYTRUDA への局所的な胃腸曝露及び限定的な全身曝露の影響は不明である。授乳中の乳児に重篤な有害事象が発現する可能性があるため、本剤の投与中及び投与終了後4ヵ月間は授乳を中止することを助言すること。

8.3　妊娠する可能性のある女性及び男性への使用

妊娠検査

KEYTRUDA 投与開始前に、妊娠する可能性のある女性の妊娠状態について確認すること［特殊集団への投与（8.1）参照］。

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避妊

KEYTRUDA を妊婦に投与した場合、胎児に危険を及ぼす可能性がある［警告及び使用上の注意（5.5）及び特殊集団への投与（8.1）参照］。妊娠する可能性のある女性には、本剤の投与中及び投与終了後4ヵ月間において有効な避妊方法を用いることを助言すること。

8.4　小児への使用

小児の悪性黒色腫、古典的ホジキンリンパ腫、原発性縦隔大細胞型 B 細胞リンパ腫、メルケル細胞癌、MSI-High 又は MMR 欠損を有する癌及び TMB-High 癌患者における KEYTRUDA 単独投与の安全性及び有効性は確立している。これらの適応症をきたす患者における本剤の使用は、成人を対象とした適切かつ十分に管理された試験のエビデンスに加え、小児患者における薬物動態及び安全性の追加データによって裏付けられている［副作用（6.1）、臨床薬理学（12.3）、臨床試験（14.1、14.4、14.5、14.7、14.14、14.17）参照］。

KEYNOTE-051試験では、進行性悪性黒色腫、リンパ腫又は PD-L1陽性固形がんの小児患者173例（生後6ヵ月から12歳未満が65例、12～17歳が108例）に KEYTRUDA 2 mg/kg を3週間間隔で投与した。投与期間の中央値は2.1ヵ月（範囲：1日～25ヵ月）であった。成人患者と比べ小児患者で10%以上発現割合が高かった副作用は、発熱（33%）、嘔吐（29%）、頭痛（25%）、腹痛（23%）、リンパ球数減少（13%）及び白血球数減少（11%）であった。成人患者と比べ小児患者で10%以上発現割合が高かった臨床検査値異常は、白血球減少症（31%）、好中球減少症（28%）、血小板減少症（22%）及び Grade 3の貧血（17%）であった。

小児患者に本剤を投与した際の安全性及び有効性は、その他の承認された適応では確立されていない［効能・効果（1）参照］。

8.5　高齢者への使用

臨床試験で KEYTRUDA を投与された悪性黒色腫、非小細胞肺癌、頭頸部扁平上皮癌及び尿路上皮癌の患者3781例のうち、65歳以上の患者の割合は48%であり、75歳以上の患者の割合は17%であった。高齢患者及び非高齢患者での安全性又は有効性に概して差異は認められなかった。

臨床試験で KEYTRUDA を投与された古典的ホジキンリンパ腫成人患者389例のうち、65歳以上の患者は46例（12%）であった。重篤な副作用の発現割合は、65歳以上の患者（50%）で65歳未満の患者（24%）よりも高かった。古典的ホジキンリンパ腫に関する KEYTRUDA の臨床試験では65歳以上の患者の数が十分でなく、非高齢患者との間で有効性に差異があるか否かは判断できなかった。

KEYNOTE-091試験で KEYTRUDA の投与を受けた外科的完全切除及びプラチナ製剤化学療法後の IB 期（T2a≥4 cm）、II 期、又は IIIA 期の成人の非小細胞肺癌患者506例のうち、242例（48%）が65歳以上であった。高齢患者及び非高齢患者での安全性又は有効性に概して差異は認められなかった。

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KEYNOTE-355試験で KEYTRUDA とパクリタキセル、nab-パクリタキセル又はゲムシタビン及びカルボプラチンとの併用投与を受けたトリプルネガティブ乳癌成人患者596例のうち、65歳以上の患者は137例（23%）であった。高齢患者及び非高齢患者での安全性又は有効性に概して差異は認められなかった。

KEYNOTE-775試験で KEYTRUDA とレンバチニブとの併用投与を受けた子宮体癌成人患者406例のうち、65歳以上の患者は201例（50%）であった。高齢患者及び非高齢患者での安全性又は有効性に概して差異は認められなかった。

KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた局所進行性又は転移性の尿路上皮癌患者564例のうち、65～74歳の患者は44%（247例）、75歳以上は26%（144例）であった。65歳以上の患者及び65歳未満の患者での安全性又は有効性に概して差異は認められなかった。KEYTRUDA とエンホルツマブベドチンとの併用投与を受けた75歳以上の患者は、75歳未満の患者と比較して、死亡に至った有害事象の発現割合が高かった。死亡に至った有害事象の発現割合は、75歳未満では4%、75歳以上では7%であった。

KEYNOTE-426試験で KEYTRUDA とアキシチニブの併用投与群に割り付けた患者432例のうち、65歳以上の患者は40%であった。65歳以上の患者及び65歳未満の患者での安全性又は有効性に概して差異は認められなかった。

KEYNOTE-A18試験で KEYTRUDA と CRT との併用療法を受けた FIGO 2014進行期分類の IIIーIVA 期子宮頸癌の成人患者292例のうち、42例（14%）が65歳以上であった。高齢患者及び非高齢患者での安全性又は有効性に概して差異は認められなかった。

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1.6.2.1.2　EU 添付文書の概要（和訳）

EU 添付文書の概要を以下に示す。概要の項目番号は原文の項目番号にあわせた。

販売名／販売会社名

KEYTRUDA/Merck Sharp & Dohme B.V.

剤型・含量

2　剤形・含量

注射用溶液製剤100 mg/4 mL バイアル

溶解溶液1 mL 中ペムブロリズマブとして25 mg 含有

効能・効果

4　臨床上の特徴

4.1　効能・効果

悪性黒色腫

KEYTRUDA（pembrolizumab）の単独投与は、成人患者及び12歳以上の青少年患者の進行性悪性黒色腫（切除不能又は転移性）の治療を適応とする。

KEYTRUDA の単独投与は、ⅡB、ⅡC 又はⅢ期の悪性黒色腫に対する完全切除後の成人患者及び12歳以上の青少年患者への術後補助療法を適応とする［薬力学的特性（5.1）参照］。

非小細胞肺癌（NSCLC）

KEYTRUDA とプラチナ製剤化学療法との併用による術前補助療法及びその後の KEYTRUDA の単独投与による術後補助療法は、再発リスクが高い切除可能な非小細胞肺癌成人患者の治療を適応とする［選択基準については、薬力学的特性（5.1）参照］。

KEYTRUDA の単独投与は、非小細胞肺癌に対する完全切除及びプラチナ製剤化学療法後の再発リスクが高い成人患者の術後補助療法を適応とする［選択基準については、薬力学的特性（5.1）参照］。

KEYTRUDA の単独投与は、腫瘍細胞に PD-L1高発現［Tumor Proportion Score （腫瘍細胞のうち PD-L1発現陽性細胞の割合）：TPS≥50%］が確認され、EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性ではない、転移性の非小細胞肺癌の成人患者の一次治療を適応とする。

KEYTRUDA とペメトレキセド及びプラチナ製剤化学療法の併用投与は、EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性ではない、転移性の非扁平上皮非小細胞肺癌の成人患者の一次治療を適応とする。

KEYTRUDA とカルボプラチン及びパクリタキセル又は nab-パクリタキセルの併用投与は、転移性の扁平上皮非小細胞肺癌の成人患者の一次治療を適応とする。

KEYTRUDA の単独投与は、腫瘍細胞に PD-L1発現陽性（TPS≥1%）が確認された局所進行又は転移性の非小細胞肺癌を有し、化学療法による治療歴が1つ以上ある成人患者への治療を適応とする。EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性の患者については、KEYTRUDA の投与前に分子標的薬の投与を受けた患者とする。

古典的ホジキンリンパ腫（cHL）

KEYTRUDA の単独投与は、自家造血幹細胞移植（ASCT）が無効な、又は自家造血幹細胞移植非適応で前治療を2レジメン以上受けた、再発又は難治性の古典的ホジキンリンパ腫を有する成人及び3歳以上の小児の患者への治療を適応とする。

尿路上皮癌

KEYTRUDA の単独投与は、プラチナ製剤併用化学療法後の局所進行性又は転移性の尿路上皮癌を有する成人患者への治療を適応とする［薬力学的特性（5.1）参照］。

KEYTRUDA の単独投与は、腫瘍細胞に PD-L1発現陽性［Combined Positive Score（CPS）≥10］が確認されたシスプラチン不耐容の局所進行性又は転移性の尿路上皮癌を有する成人患者への治療を適応とする［薬力学的特性（5.1）参照］。

頭頸部扁平上皮癌（HNSCC）

KEYTRUDA の単独投与又はプラチナ製剤及び5-フルオロウラシル（5-FU）の化学療法との併用投与は、腫瘍細胞に PD-L1発現陽性（CPS≥1）が確認された転移性又は切除不能の再発頭頸部扁平上皮癌を有する成人患者への一次治療を適応とする［薬力学的特性（5.1）参照］。

KEYTRUDA の単独投与は、腫瘍細胞に PD-L1高発現（TPS≥50%）が確認され、プラチナ製剤併用化学療法による治療中及び治療後に疾患進行が認められた再発又は転移性の頭頸部扁平上皮癌を有する成人患者への治療を適応とする［薬力学的特性（5.1）参照］。

腎細胞癌（RCC）

KEYTRUDA とアキシチニブの併用投与は、進行性腎細胞癌の成人患者の一次治療を適応とする［薬力学的特性（5.1）参照］。

KEYTRUDA とレンバチニブの併用投与は、進行性腎細胞癌の成人患者の一次治療を適応とする［薬力学的特性（5.1）参照］。

KEYTRUDA の単独投与は、腎摘出後又は腎摘出及び転移巣切除後に高度の再発リスクを有する腎細胞癌の成人患者の術後補助療法を適応とする［選択基準については、薬力学的特性（5.1）参照］。

MSI-High 又は MMR 欠損の癌

結腸・直腸癌（CRC）

KEYTRUDA の単独投与は、以下に該当する MSI-High 又は MMR 欠損の結腸・直腸癌を有する

成人患者を適応とする。

- 転移性の結腸・直腸癌に対する一次治療
- フッ化ピリミジン系併用療法後の切除不能又は転移性の結腸・直腸癌

非結腸・直腸癌

KEYTRUDA の単独投与は、以下に該当する MSI-High 又は MMR 欠損の腫瘍を有する成人患者を適応とする。

- 進行性又は再発性の子宮体癌で、プラチナ製剤併用化学療法による前治療中または治療後に疾患が進行し、根治手術または放射線療法の対象とならない患者
- 切除不能又は転移性の胃癌、小腸癌、又は胆道癌で、少なくとも1つの前治療中または治療後に疾患が進行している患者

食道癌

KEYTRUDA とプラチナ製剤及びフッ化ピリミジン系化学療法の併用投与は、腫瘍細胞に PD-L1 発現陽性（CPS≥10）が確認された、成人の局所進行の切除不能若しくは転移性の食道癌の一次治療を適応とする［薬力学的特性（5.1）参照］。

トリプルネガティブ乳癌（TNBC）

KEYTRUDA と化学療法の術前薬物療法としての併用投与及びその後に続く術後薬物療法としての KEYTRUDA の単独療法は、成人の局所進行又は再発リスクの高い早期トリプルネガティブ乳癌の治療を適応とする［薬力学的特性（5.1）参照］。

KEYTRUDA と化学療法の併用投与は、腫瘍細胞に PD-L1発現陽性（CPS≥10）が確認された、転移性疾患に対して化学療法による前治療を受けたことがない、成人の局所再発の切除不能又は転移性のトリプルネガティブ乳癌の治療を適応とする［薬力学的特性（5.1）参照］。

子宮体癌（EC）

KEYTRUDA とレンバチニブの併用投与は、これまでのプラチナ製剤化学療法による前治療中又は前治療後に疾患進行が認められ、根治的切除術又は放射線療法が不適応である、成人の進行性又は転移性の子宮体癌の治療を適応とする。

子宮頸癌

KEYTRUDA は、ベバシズマブ併用又は非併用の化学療法との併用療法として、PD-L1発現陽性（CPS≥1）が確認された、成人の持続、再発又は転移性の子宮頸癌の治療を適応とする。

胃腺癌又は胃食道接合部腺癌

KEYTRUDA は、トラスツズマブ、フッ化ピリミジン及びプラチナ製剤化学療法との併用療法として、腫瘍細胞に PD-L1発現陽性（CPS≥1）が確認された、成人の局所進行の切除不能又は転移性

の HER2陽性胃腺癌又は胃食道接合部腺癌の一次治療を適応とする。

KEYTRUDA は、フッ化ピリミジン及びプラチナ製剤化学療法との併用療法として、腫瘍細胞に PD-L1発現陽性（CPS≥1）が確認された、成人の局所進行の切除不能又は転移性の HER2陰性胃腺癌又は胃食道接合部腺癌の一次治療を適応とする［薬力学的特性（5.1）参照］。

胆道癌（BTC）

KEYTRUDA とゲムシタビン及びシスプラチンとの併用投与は、成人の局所進行の切除不能又は転移性の胆道癌の一次治療を適応とする。

用法・用量

4.2　用法・用量

治療にあたっては、癌治療の経験を有する専門医の監督のもとで開始すること。

PD-L1発現検査

効能・効果に規定されている場合、検証された検査により PD-L1発現陽性が確認された患者を KEYTRUDA 投与の対象とする［効能・効果（4.1）、警告及び使用上の注意（4.4）、副作用（4.8）及び薬力学的特性（5.1）参照］。

MSI／MMR 判定検査

適応症で定められている場合は、KEYTRUDA を投与する患者を選択するため、検証された検査により腫瘍細胞の MSI-High／MMR 欠損を判定すること［効能・効果（4.1）及び薬力学的特性（5.1）参照］。

用法・用量

成人に対する推奨用量は、200 mg を3週間間隔又は400 mg を6週間間隔で30分間かけて点滴静注する。

古典的ホジキンリンパ腫を有する3歳以上の小児患者又は悪性黒色腫を有する12歳以上の青少年患者に対する単独投与時の推奨用量は、2 mg/kg（最大200 mg）を3週間間隔で30分間かけて点滴静注する。

KEYTRUDA の併用投与時の使用方法は、KEYTRUDA の添付文書に記載する併用療法を参照すること。

疾患進行又は許容できない副作用の発現（及び該当の適応症に治療最長期間の記載がある場合はその期間）まで使用を続けること。非定型反応（初期の一過性の腫瘍拡大又は最初の数ヵ月以内に小さな新病変発現後、腫瘍縮小）が認められている。疾患進行の初期症状が認められた臨床的に安定している患者では、疾患進行が確定するまで投与を継続することが推奨される。

悪性黒色腫、非小細胞肺癌、又は腎細胞癌に対する術後補助療法では、再発又は許容できない副作用の発現まで、あるいは最長1年間の投与まで使用を続けること。

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切除可能な非小細胞肺癌に対する術前・術後補助療法では、術前補助療法として KEYTRUDA 200 mg を3週間間隔で4回若しくは400 mg を6週間間隔で2回、又は、根治手術不適応な疾患の進行若しくは許容できない副作用の発現まで化学療法と併用投与すること。その後、術後補助療法として KEYTRUDA 200 mg を3週間間隔で13回若しくは400 mg を6週間間隔で7回、又は、疾患の再発若しくは許容できない副作用の発現まで単独投与すること。KEYTRUDA と化学療法との併用による術前補助療法と関連のある根治手術不適応な疾患の進行又は許容できない副作用の発現が生じた場合は、術後補助療法として KEYTRUDA の単独投与を行わないこと。

トリプルネガティブ乳癌に対する術前・術後薬物療法では、術前薬物療法として KEYTRUDA 200 mg を3週間間隔で8回若しくは400 mg を6週間間隔で4回、又は、根治手術不適応な疾患の進行若しくは許容できない副作用の発現まで化学療法と併用投与すること。その後、術後薬物療法として KEYTRUDA 200 mg を3週間間隔で9回若しくは400 mg を6週間間隔で5回、又は、疾患の再発若しくは許容できない副作用の発現まで単独投与すること。KEYTRUDA と化学療法との併用による術前薬物療法と関連のある根治手術不適応な疾患の進行又は許容できない副作用の発現が生じた場合は、術後薬物療法として KEYTRUDA の単独投与を行わないこと。

休薬又は中止［警告及び使用上の注意（4.4）参照］

KEYTRUDA の減量は推奨されない。副作用の管理を目的とする KEYTRUDA の休薬又は中止は[表 1.6.2-57]を参照のこと。

表 1.6.2-57　　推奨される KEYTRUDA の投与の変更

免疫関連の副作用	程度	投与の変更
肺臓炎	Grade 2の肺臓炎	Grade 1以下に回復するまで休薬†
	Grade 3若しくは4の肺臓炎、又は Grade 2の肺臓炎の再発	中止
大腸炎	Grade 2又は3の大腸炎	Grade 1以下に回復するまで休薬†
	Grade 4の大腸炎又は Grade 3の大腸炎の再発	中止
腎炎	Grade 2の腎炎でクレアチニンが基準値上限の1.5倍超～3倍	Grade 1以下に回復するまで休薬†
	Grade 3以上の腎炎でクレアチニンが基準値上限の3倍超	中止
内分泌障害	Grade 2の副腎機能不全及び下垂体炎	ホルモン補充療法で管理可能となるまで休薬
	Grade 3又は4の副腎機能不全又は症候性下垂体炎 Grade 3以上の高血糖（血糖値：250 mg/dL 超又は13.9 mmol/L 超）又はケトアシドーシスに関連した1型糖尿病 Grade 3以上の甲状腺機能亢進症	Grade 1以下に回復するまで休薬† Grade 2以下に回復した Grade 3又は4の内分泌障害で、必要であればホルモン補充療法で管理されている患者は、必要に応じて、副腎皮質ホルモン剤漸減後、本剤の投与の継続を考慮すること。それ以外の場合は投与を中止すること。
	甲状腺機能低下症	甲状腺機能低下症は、休薬することなくホルモン補充療法で管理可能である。
肝炎 注：KEYTRUDA と	肝炎で AST 若しくは ALT が基準値上限の3倍超～5倍、又は総ビリルビンが基準値上限の1.5倍超～3倍（Grade 2）	Grade 1以下に回復するまで休薬†

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アキシチニブの併用投与を受けた腎細胞癌患者の肝酵素増加については、本表下の投与指針を参照	肝炎で AST 若しくは ALT が基準値上限の5倍超、又は総ビリルビンが基準値上限の3倍超（Grade 3以上）	中止
	ベースライン時の Grade 2の AST 又は ALT の上昇を伴う肝転移の場合、肝炎で AST 又は ALT が50%以上上昇し、1週間以上持続する	中止
皮膚反応	Grade 3の皮膚反応、又はスティーヴンス・ジョンソン症候群（SJS）又は中毒性表皮壊死融解症（TEN）が疑われる場合	Grade 1以下に回復するまで休薬†
	Grade 4の皮膚反応、又はスティーヴンス・ジョンソン症候群又は中毒性表皮壊死融解症が確定した場合	中止
その他の免疫関連の副作用	程度及び副作用の種類に基づく（Grade 2又は3）	Grade 1以下に回復するまで休薬†
	Grade 3又は4の心筋炎 Grade 3又は4の脳炎 Grade 3又は4のギラン・バレー症候群	中止
	Grade 4の免疫関連の副作用、又は Grade 3の免疫関連の副作用の再発	中止
Infusion-related reaction	Grade 3又は4の Infusion-related reaction	中止
Grade 分類は NCI CTCAE v4.0に基づく。 † KEYTRUDA の最終投与から12週間以内に副作用が Grade 1以下に回復しない場合、又は12週間以内に副腎皮質ホルモン剤の用量を10 mg／日以下（プレドニゾロン換算）に漸減できない場合、KEYTRUDA の投与を中止すること。		

免疫関連の心筋炎の既往がある患者に、KEYTRUDA の投与を再開した場合の安全性は不明である。

[表 1.6.2-57]に規定がない限り、Grade 4又は Grade 3の免疫関連の副作用の再発の場合には、KEYTRUDA（単独投与又は併用投与）の投与を中止すること。

古典的ホジキンリンパ腫患者に Grade 4の血液毒性が発現した場合のみ、副作用が Grade 1以下に回復するまで、KEYTRUDA の投与を休薬すること。

腎細胞癌患者に対する KEYTRUDA とアキシチニブの併用投与

腎細胞癌患者に対する KEYTRUDA とアキシチニブの併用投与における、アキシチニブの投与方法は、アキシチニブの添付文書を参照すること。KEYTRUDA と併用する場合、6週間以上投与後に、アキシチニブの初回用量5 mg からの増量を検討することができる［薬力学的特性（5.1）参照］。

<u>KEYTRUDA とアキシチニブの併用投与を受けた腎細胞癌患者における肝酵素の上昇：</u>

- ALT 又は AST が基準値上限の3倍以上10倍未満で、かつ総ビリルビンが基準値上限の2倍に達していない場合、それらの副作用が Grade 1以下に回復するまで KEYTRUDA とアキシチニブを休薬する。副腎皮質ホルモン剤の投与を考慮すること。回復後、いずれか一剤の再開又は両剤の順次再開を考慮する。アキシチニブの再開にあたっては、アキシチニブの添付文書に基づき減量を考慮する。

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- ALT 又は AST が基準値上限の10倍以上、又は3倍超かつ総ビリルビンが基準値上限の2倍以上の場合、KEYTRUDA 及びアキシチニブの両剤の投与を中止し、副腎皮質ホルモン剤の投与を考慮すること。

KEYTRUDA とレンバチニブの併用投与

KEYTRUDA とレンバチニブを併用投与する際には、一方又は両方の薬剤を適切に投与中断する必要がある。KEYTRUDA とレンバチニブの併用投与において、レンバチニブの添付文書の規定に従い、レンバチニブを休薬、減量、中止すること。KEYTRUDA の減量は推奨しない。

KEYTRUDA の治療を受ける患者には患者カードを提供し、KEYTRUDA のリスクについて知らせる（製品リーフレットも参照する）こと。

特別な患者集団

高齢者

65歳以上の患者における用量調節は必要ない。[警告及び使用上の注意（4.4）及び薬力学的特性（5.1）参照]

腎機能障害

軽度から中等度の腎機能障害を有する患者における用量調節は必要ない。重度腎機能障害患者を対象とした KEYTRUDA の検討は行われていない。[警告及び使用上の注意（4.4）及び薬力学的特性（5.1）参照]

肝機能障害

軽度から中等度の肝機能障害を有する患者における用量調節は必要ない。重度の肝機能障害患者を対象とした KEYTRUDA の検討は行われていない。[警告及び使用上の注意（4.4）及び薬物動態特性（5.2）参照]

小児

悪性黒色腫又は cHL の小児患者を除き、18歳未満の小児における KEYTRUDA の有効性及び安全性は確立していない。現時点で得られている結果は、副作用（4.8）、薬力学的特性（5.1）及び薬物動態特性（5.2）に記載されている。

投与方法

KEYTRUDA は点滴静注用製剤である。30分間かけて静脈内投与すること。

KEYTRUDA は静脈内注射又は静脈内ボーラス投与しないこと。

KEYTRUDA を静注用化学製剤と併用投与する際は、先に KEYTRUDA を投与すること。

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投与前の本剤の調製方法は、［廃棄およびその他の取り扱いに関する特別な注意事項（6.6）］を参照すること。

禁忌

4.3　禁忌

本剤の有効成分又は添加物に対し過敏症の既往歴のある患者［添加物一覧（6.1）参照］。

警告

4.4　警告及び使用上の注意

トレーサビリティ

生物学的製剤のトレーサビリティ向上のため、投与した薬剤の名称とロット番号は明確に記録すること。

PD-L1の発現状況の評価

偽陰性又は偽陽性判定を最小限に抑えるため、十分に検証された確実な方法で腫瘍の PD-L1発現を評価することが重要である。

免疫関連の副作用

KEYTRUDA の投与を受けた患者で、重度及び死亡例も含む免疫関連の副作用が発現している。KEYTRUDA の投与を受けた患者で認められた免疫関連の副作用のほとんどが可逆的であり、KEYTRUDA の休薬、副腎皮質ホルモン剤及び／又は支持療法により対処可能であった。また、免疫関連の副作用は KEYTRUDA の最終投与後にも認められた。同時に複数の臓器に影響を及ぼす免疫関連の副作用が発現することもある。

免疫関連の副作用が疑われる場合、適切な検査等で病因を確認し、他の原因を除外すること。副作用の程度に基づき、本剤を休薬し、副腎皮質ホルモン剤を投与すること。Grade 1以下に回復した場合、1ヵ月以上かけて副腎皮質ホルモン剤を漸減する。臨床試験のデータはわずかであるが、副腎皮質ホルモン剤で免疫関連の副作用を管理できなかった場合には、その他の全身性の免疫抑制剤の投与を検討すること。

副作用が Grade 1以下に回復し、副腎皮質ホルモン剤の用量を10 mg／日以下（プレドニゾロン換算）に漸減できた場合、KEYTRUDA の最終投与後12週間以内に投与を再開する。

Grade 3の免疫関連の副作用が再発した場合及び Grade 4の免疫関連の副作用（ホルモン補充療法で管理された内分泌障害を除く）が発現した場合、KEYTRUDA を中止すること［用法・用量（4.2）及び副作用（4.8）参照］。

免疫関連の肺臓炎

KEYTRUDA の投与を受けた患者で、肺臓炎が発現した［副作用（4.8）参照］。肺臓炎の徴候及び症状をモニタリングすること。肺臓炎が疑われる場合、放射線画像により確認し、他の原因を

除外すること。Grade 2以上の場合には、副腎皮質ホルモン剤（初回用量はプレドニゾロン換算1～2 mg/kg/日、その後漸減）を投与すること。Grade 2の場合は本剤を休薬し、Grade 3又は4の肺臓炎、若しくはGrade 2の肺臓炎が再発した場合は本剤を中止すること［用法・用量（4.2）参照］。

免疫関連の大腸炎

KEYTRUDA の投与を受けた患者で、大腸炎が発現した［副作用（4.8）参照］。大腸炎の徴候及び症状をモニタリングし、他の原因を除外すること。Grade 2以上の場合には、副腎皮質ホルモン剤（初回用量はプレドニゾロン換算1～2 mg/kg/日、その後漸減）を投与すること。Grade 2又は3の場合には本剤を休薬し、Grade 4又は Grade 3再発時の場合には本剤を中止すること［用法・用量（4.2）参照］。消化管穿孔の潜在的リスクについて考慮すること。

免疫関連の肝炎

KEYTRUDA の投与を受けた患者で、肝炎が発現した［副作用（4.8）参照］。肝機能検査値の変動（投与開始時、投与中定期的に、及び臨床評価に基づいて）及び肝炎の症状をモニタリングし、他の原因を除外すること。副腎皮質ホルモン剤（Grade 2の場合、初回用量はプレドニゾロン換算0.5～1 mg/kg/日、Grade 3以上の場合、初回用量はプレドニゾロン換算1～2 mg/kg/日、その後漸減）を投与し、肝酵素上昇の程度に基づき本剤を休薬又は中止すること［用法・用量（4.2）参照］。

免疫関連の腎炎

KEYTRUDA の投与を受けた患者で、腎炎が発現した［副作用（4.8）参照］。腎機能検査値の変動をモニタリングし、腎機能障害の他の原因を除外すること。Grade 2以上の場合には、副腎皮質ホルモン剤（初回用量はプレドニゾロン換算1～2 mg/kg/日、その後漸減）を投与し、クレアチニン増加の程度に基づき Grade 2の場合には本剤を休薬し、Grade 3又は4の腎炎の場合には本剤を中止すること［用法・用量（4.2）参照］。

免疫関連の内分泌障害

KEYTRUDA の投与を受けた患者で、重度の内分泌障害（副腎機能不全、下垂体炎、1型糖尿病、糖尿病性ケトアシドーシス、甲状腺機能低下症及び甲状腺機能亢進症を含む）が発現した。

免疫関連の内分泌障害の場合、長期的なホルモン補充療法が必要なことがある。

KEYTRUDA の投与を受けた患者で、副腎機能不全（初発及び続発性）及び下垂体炎が発現した［副作用（4.8）参照］。副腎機能不全及び下垂体炎（下垂体機能低下症を含む）の徴候及び症状をモニタリングし、他の原因を除外すること。臨床的に必要であれば、副腎機能不全の治療に副腎皮質ホルモン剤やその他のホルモン補充療法を実施すること。Grade 2の副腎機能不全及び下垂体炎はホルモン補充療法で管理ができるまで本剤を休薬すること。Grade 3又は4の副腎機能不全又は症候性下垂体炎が発現した場合には、本剤は休薬又は中止すること。必要に応じて、副腎皮質ホルモン剤の漸減後、本剤の継続を考慮すること［用法・用量（4.2）参照］。下垂体機能及びホルモン値をモニタリングし、適切なホルモン補充療法を実施すること。

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KEYTRUDA の投与を受けた患者で、糖尿病性ケトアシドーシスを含む1型糖尿病が発現した［副作用（4.8）参照］。高血糖並びに糖尿病の他の徴候及び症状をモニタリングすること。1型糖尿病ではインスリンを投与し、Grade 3以上の高血糖又はケトアシドーシスを伴う1型糖尿病の場合は代謝調節ができるまで本剤を休薬すること［用法・用量（4.2）参照］。

KEYTRUDA の投与を受けた患者で、甲状腺障害（甲状腺機能低下症、甲状腺機能亢進症及び甲状腺炎を含む）が発現した。甲状腺障害は治療中いつでも発症する可能性がある。甲状腺機能低下症は、放射線療法歴のある頭頸部扁平上皮癌患者でより高頻度に報告されている。患者の甲状腺機能の変化（投与開始時、投与中定期的に、及び臨床評価に基づいて）並びに甲状腺障害の徴候及び症状をモニタリングすること。甲状腺機能低下症は休薬することなく、副腎皮質ホルモン剤の投与なしで、補充療法で管理が可能である。甲状腺機能亢進症は臨床症状の管理が可能である。Grade 3以上の甲状腺機能亢進症の場合には、Grade 1以下に回復するまで本剤を休薬すること。甲状腺機能及びホルモン値をモニタリングし、適切なホルモン補充療法を実施すること。

ホルモン補充療法で管理され Grade 2以下に回復した Grade 3又は4の内分泌障害の場合には、必要に応じて、副腎皮質ホルモン剤の漸減後、本剤の投与の継続を考慮するか、投与を中止すること［用法・用量（4.2）及び副作用（4.8）参照］。

免疫関連の皮膚の副作用

KEYTRUDA の投与を受けた患者で、重度の免疫関連の皮膚反応が発現した［副作用（4.8）参照］。重度の皮膚反応の疑いがある場合は、患者を注意深くモニタリングし、他の原因を除外すること。その程度に基づき、Grade 3の皮膚反応の場合は Grade 1以下に軽快するまで本剤を休薬、Grade 4の皮膚反応の場合は本剤を中止し、副腎皮質ホルモン剤を投与すること［用法・用量（4.2）参照］。

KEYTRUDA の投与を受けた患者で、スティーヴンス・ジョンソン症候群及び中毒性表皮壊死融解症が発現した［副作用（4.8）参照］。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の疑いがある場合は、本剤の投与を休薬し、専門のケアを実施するために専門医による診断及び治療を患者に勧めること。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の診断が確定した場合は、本剤の投与を中止すること［用法・用量（4.2）参照］。

他の免疫刺激抗がん剤を用いた前治療により、重度又は生命を脅かす皮膚の副作用を発現した患者に本剤の投与を検討する際には注意が必要である。

その他の免疫関連の副作用

臨床試験又は市販後の使用において、以下のその他の臨床的に重要な免疫関連の副作用が発現した（ぶどう膜炎、関節炎、筋炎、心筋炎、膵炎、ギラン・バレー症候群、筋無力症候群、溶血性貧血、サルコイドーシス、脳炎、脊髄炎、血管炎、硬化性胆管炎、胃炎、非感染性膀胱炎及び副甲状腺機能低下症）［用法・用量（4.2）及び副作用（4.8）参照］。

副作用の程度及び種類に基づき、Grade 2又は3の場合は本剤を休薬し、副腎皮質ホルモン剤を投

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与すること。

副作用が Grade 1以下に軽快し、副腎皮質ホルモン剤の用量を10 mg／日以下（プレドニゾロン換算）に漸減できた場合、本剤の最終投与後12週間以内に投与を再開する。

Grade 3の免疫関連の副作用が再発した場合及び Grade 4の免疫関連の副作用が発現した場合、本剤を休薬すること。

Grade 3又は4の心筋炎、脳炎又はギラン・バレー症候群が発現した場合、本剤を中止すること［用法・用量（4.2）及び副作用（4.8）参照］。

臓器移植関連の副作用

固形臓器移植後拒絶反応

市販後の使用において、PD-1阻害剤の投与を受けた患者で固形臓器移植後拒絶反応が報告されている。本剤の投与は、固形臓器移植レシピエントに対する移植後拒絶反応のリスクを増加させる可能性がある。これらの患者については、KEYTRUDA 投与のベネフィットとリスク（移植後拒絶反応の可能性）を十分に考慮してから投与を行うこと。

同種造血幹細胞移植（HSCT）に伴う合併症

KEYTRUDA 投与後の同種造血幹細胞移植

KEYTRUDA の投与後に同種造血幹細胞移植を受けた古典的ホジキンリンパ腫患者で、移植片対宿主病（GVHD）及び肝中心静脈閉塞症（VOD）が発現した。さらなるデータが得られるまで、造血幹細胞移植のベネフィットとリスク（移植関連の合併症）を慎重に考慮して、状況に応じて KEYTRUDA の投与を行うこと［副作用（4.8）参照］。

KEYTRUDA 投与前の同種造血幹細胞移植

同種造血幹細胞移植歴のある患者で、KEYTRUDA の投与後に死亡に至る事象を含む急性の移植片対宿主病が報告された。移植後に移植片対宿主病を発現した患者において、KEYTRUDA の投与後に移植片対宿主病のリスクが増加する可能性がある。同種造血幹細胞移植歴のある患者については、KEYTRUDA のベネフィットとリスク（移植片対宿主病の可能性）を考慮すること。

Infusion-related reaction

KEYTRUDA の投与を受けた患者で、過敏症及びアナフィラキシーを含めた重度の Infusion-related reaction が発現した［副作用（4.8）参照］。Grade 3又は4の Infusion reaction が認められた場合は注入を中止し、本剤を中止すること［用法・用量（4.2）参照］。Grade 1又は2の Infusion reaction が認められた場合は、注意深く観察して注入を継続し、解熱剤及び抗ヒスタミン剤による前投薬を考慮すること。

KEYTRUDA と化学療法の併用

75歳以上の患者に KEYTRUDA と化学療法の併用投与を行う場合は、個々の症例の状況に応じ

てリスク／ベネフィットバランスを慎重に考慮した上で、注意深く使用すること［薬力学的特性（5.1）参照］。

疾患特異的な注意事項

プラチナ製剤併用化学療法による既治療の尿路上皮癌患者に対する KEYTRUDA の使用

予後不良及び／又は進行が早い疾患を有する患者に KEYTRUDA の投与を開始する前に、KEYTRUDA による治療効果が遅れて発現する可能性を考慮しなければならない。尿路上皮癌では、投与開始後2ヵ月以内の死亡例数は、化学療法群と比較して KEYTRUDA 群で高かった［薬力学的特性（5.1）参照］。早期死亡と関連する因子は、前治療のプラチナ製剤併用化学療法における疾患の進行速度及び肝転移であった。

腫瘍細胞に PD-L1発現陽性（CPS≥10）が確認された、シスプラチン併用化学療法不耐容の尿路上皮癌患者に対する KEYTRUDA の使用

KEYNOTE-052試験の患者集団の患者背景及び予後特性には、比較試験（KEYNOTE-361試験）でベネフィットが評価されているカルボプラチンの併用療法に適応となる患者が含まれていた。KEYNOTE-361試験において、投与開始後6ヵ月以内の死亡例数は、化学療法群と比較して KEYTRUDA 単独投与群で高く、その後に長期生存が観察された［薬力学的特性（5.1）参照］。早期死亡と関連する因子は特定されなかった。カルボプラチンの併用化学療法に適応となる尿路上皮癌患者に KEYTRUDA の投与を開始する前に、KEYTRUDA による治療効果が遅れて発現する可能性を考慮しなければならない。KEYNOTE-052試験には、無作為化データが利用可能ではない、単独化学療法に適応となる患者も含まれていた。さらに、化学療法に不耐容と判断される虚弱な患者（ECOG PS が3の患者など）における安全性及び有効性のデータは得られていない。そのため、これらの患者に KEYTRUDA の投与を行う場合は、個々の症例の状況に応じてリスク／ベネフィットバランスを慎重に考慮した上で、注意深く使用すること。

未治療の非小細胞肺癌患者に対する KEYTRUDA の使用

全般的に、KEYTRUDA を併用投与した場合、併用投与の各薬剤の成分の寄与を反映して KEYTRUDA 単独投与又は化学療法単独よりも有害事象の発現割合が高かった［用法・用量（4.2）及び副作用（4.8）参照］。KEYTRUDA と化学療法との併用投与と KEYTRUDA の単独投与について、直接的に比較できるデータはない。

腫瘍細胞に PD-L1発現陽性が確認された未治療の非小細胞肺癌患者に投与を行う前に、利用可能な治療法（KEYTRUDA 単独投与又は KEYTRUDA と化学療法との併用投与）の潜在的なリスク／ベネフィットバランスを考慮しなければならない。

KEYNOTE-042試験において、投与開始後4ヵ月以内の死亡例数は、化学療法群と比較して KEYTRUDA 単独投与群で高く、その後に長期生存が観察された［薬力学的特性（5.1）参照］。

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未治療の頭頸部扁平上皮癌患者に対する KEYTRUDA の使用

全般的に、KEYTRUDA を併用投与した場合、併用投与の各薬剤の成分の寄与を反映して KEYTRUDA 単独投与又は化学療法単独よりも有害事象の発現割合が高かった［副作用（4.8）参照］。

腫瘍細胞に PD-L1発現陽性が確認された頭頸部扁平上皮癌患者に投与を行う前に、利用可能な治療法（KEYTRUDA 単独投与又は KEYTRUDA と化学療法との併用投与）のリスク／ベネフィットバランスを考慮しなければならない［薬力学的特性（5.1）参照］。

進行性又は再発性の MSI-High／MMR 欠損の子宮体癌患者に対する KEYTRUDA の使用

KEYTRUDA をレンバチニブと併用投与した場合と KEYTRUDA を単独投与した場合を直接比較した結果はない。進行性又は再発性の MSI-High／MMR 欠損の子宮体癌患者に投与を行う前に、利用可能な治療法（KEYTRUDA 単独投与又は KEYTRUDA とレンバチニブとの併用投与）のリスク／ベネフィットバランスを考慮しなければならない。

悪性黒色腫患者に対する術後補助療法における KEYTRUDA の使用

重度かつ重篤な副作用の発現割合の増加傾向が、75歳以上の患者で認められた。75歳以上の患者での悪性黒色腫に対する術後補助療法における KEYTRUDA の安全性データは限られている。

腎細胞癌患者に対する一次治療としての KEYTRUDA とアキシチニブの併用

進行性腎細胞癌患者において、KEYTRUDA とアキシチニブを併用投与した際に、想定された発現割合よりも高い Grade 3及び4の ALT 増加及び AST 増加が報告されている［副作用（4.8）参照］。投与開始前及び投与期間中は定期的に肝酵素をモニタリングすること。単独投与時よりも、肝酵素のモニタリングをより頻回に行うことを考慮する。両剤の医学的管理についてのガイドラインに従うこと［用法・用量（4.2）及びアキシチニブの添付文書を参照］。

MSI-High／MMR 欠損の結腸・直腸癌患者に対する一次治療としての KEYTRUDA の使用

KEYNOTE-177試験において、投与開始後4ヵ月間の全生存イベントのハザード比は、化学療法群と比較して KEYTRUDA 群で高く、その後に長期生存が観察された［薬力学的特性（5.1）参照］。

胆道癌患者に対する一次治療としての KEYTRUDA の使用

胆道癌患者において胆管炎及び胆道感染は稀ではない。胆管炎関連事象は、KEYNOTE-966試験の両投与群で報告された［KEYTRUDA と化学療法との併用群では11.2%（59例）、プラセボと化学療法との併用群では10.3%（55例）］。KEYNOTE-966試験では、胆管ステント及びドレーンを留置していた患者（74例）で胆管炎及び胆道感染のリスクが高かった［KEYTRUDA と化学療法との併用群で39.4%（13例）、プラセボと化学療法との併用群で29.3%（12例）］。投与開始前及び投与開始後は定期的に、胆管炎又は胆道感染の発現の有無について、胆道癌患者（特に胆管ステント留置患者）を注意深くモニタリングすること。

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臨床試験から除外された患者

活動性の中枢神経系（CNS）への転移を有する患者、ECOG PS ≥2の患者（尿路上皮癌及び腎細胞癌を除く）、HIV、B 型肝炎又は C 型肝炎ウイルスに感染している患者（胆道癌を除く）、活動性全身性自己免疫疾患を有する患者、間質性肺疾患を有する患者、副腎皮質ホルモン剤の全身投与を要する肺臓炎の既往歴のある患者、その他のモノクローナル抗体に対する重度の過敏症の既往歴のある患者、免疫抑制剤の投与を受けている患者、イピリムマブによる治療で重度の免疫関連の副作用［Grade 4の副作用又は12週を超えて副腎皮質ホルモン剤（1日あたりプレドニゾロン換算：10 mg 以上）を必要とする Grade 3の副作用と定義］の既往歴のある患者は、臨床試験から除外された。活動性感染症を有する患者は臨床試験から除外され、KEYTRUDA の投与前に感染症を治療することとした。KEYTRUDA の投与中に活動性感染症を発現した場合、適切な薬物療法で管理された。ベースライン時に臨床的に重要な腎機能異常（クレアチニンが基準値上限の1.5倍超）又は肝機能異常（肝転移がない場合、ビリルビンが基準値上限の1.5倍超、ALT 又は AST が基準値上限の2.5倍超）を有していた患者は臨床試験から除外された。したがって、重度の腎機能障害及び中等度から重度の肝機能障害を有する患者における情報は限られている。

眼球悪性黒色腫の患者における KEYTRUDA の安全性及び有効性データは限られている［薬力学的特性（5.1）参照］。

潜在的なリスクの増加を慎重に考慮して、これらの患者での適切な医学的管理のもと本剤を使用すること。

患者カード

KEYTRUDA の処方者は、医師情報及び Management Guideline を熟知していなければならない。処方者は KEYTRUDA の投与を受ける際のリスクについて患者と話し合わなければならない。患者には KEYTRUDA が処方されるごとに患者カードが提供される。

薬物相互作用

4.5　薬物相互作用

KEYTRUDA の薬物動態学的相互作用を評価する試験は実施していない。KEYTRUDA は異化作用により血中から消失するため、代謝に関する薬物相互作用が起こるとは考えにくい。

KEYTRUDA の薬力学的作用及び有効性に影響を及ぼす可能性があるため、本剤投与開始前に全身性副腎皮質ホルモン剤又は免疫抑制剤は投与しないこと。ただし、本剤投与開始後の免疫関連の副作用の処置には、全身性副腎皮質ホルモン剤又はその他の免疫抑制剤の使用は可能である［警告及び使用上の注意（4.4）参照］。KEYTRUDA を化学療法と併用投与する場合、制吐又は化学療法の副作用軽減目的で、副腎皮質ホルモン剤を前投与してもよい。

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妊婦及び授乳婦

4.6　生殖、妊婦及び授乳婦

妊娠する可能性のある女性への投与

妊娠する可能性のある女性は、本剤の投与中及び投与終了後少なくとも4ヵ月間は有効な避妊方法を用いること。

妊婦への投与

妊婦への KEYTRUDA の使用に関するデータは得られていない。KEYTRUDA の動物生殖試験は実施されていないが、妊娠中のマウスモデルにおいて、PD-L1シグナル伝達の阻害によって胎児への免疫寛容が無効となり、胎児消失が増加することが示されている［非臨床安全性データ（5.3）参照］。これらの結果から、KEYTRUDA の作用機序に基づき、妊娠中に本剤を投与すると、流産率や死産率の上昇などの胎児に危険を及ぼす潜在的リスクが生じる可能性が示された。ヒト免疫グロブリン G4（IgG4）は胎盤関門を通過することが報告されており、ヒト免疫グロブリン G4である KEYTRUDA は母体から発達中の胎児へ移行する可能性がある。患者の臨床状態によって本剤での治療が必要な場合を除き、妊娠中に本剤を使用しないこと。

授乳婦への投与

KEYTRUDA のヒト乳汁中への移行は明らかではない。抗体はヒト乳汁中に移行することが知られているため、新生児又は乳児へのリスクは除外できない。授乳の有益性と本剤の治療の有益性を考慮し、授乳を中止するか本剤を中止するかを決めること。

生殖

生殖への KEYTRUDA の影響を評価するための臨床データは得られていない。カニクイザルの1及び6ヵ月間反復投与毒性試験において、雌雄の生殖器に顕著な影響は認められなかった［非臨床安全性データ（5.3）参照］。

運転及び機械作業への影響

4.7　運転及び機械作業への影響

KEYTRUDA は運転及び機械作業にわずかな影響を及ぼす。KEYTRUDA の投与後にめまい及び疲労を発現した患者が報告されている［副作用（4.8）参照］。

副作用

4.8　副作用

安全性プロファイルの要約

本剤では免疫関連の副作用が最も一般的である。重度の副作用を含むほとんどが適切な薬物療法の開始後又は本剤の中止後に回復した（以下の「特定の副作用の記述」参照）。以下及び表 1.6.2-58]に含まれる発現割合は、治験担当医師による因果関係評価にかかわらず、報告されたすべての

有害事象に基づいている。

KEYTRUDA の単独投与［用法・用量（4.2）参照］

7631例の様々ながん種の患者を対象とした臨床試験で、KEYTRUDA の単独投与として4つの用量（2 mg/kg を3週間間隔、200 mg を3週間間隔、10 mg/kg を2週間間隔又は10 mg/kg を3週間間隔）の安全性を評価した。観察期間の中央値は8.5ヵ月（範囲：1日～39ヵ月）であり、高頻度に認められた有害事象は、疲労（31%）、下痢（22%）及び悪心（20%）であった。KEYTRUDA の単独投与で報告された副作用のほとんどは Grade 1又は2であった。重篤な副作用のほとんどは、免疫関連の副作用及び重度の Infusion-related reaction であった［警告及び使用上の注意（4.4）参照］。KEYTRUDA の単独投与で術後補助療法を受けた患者では、免疫関連の副作用の発現割合は37%（All Grades）、Grade 3-5は9%であり、KEYTRUDA の単独投与で転移性癌の治療を受けた患者では、免疫関連の副作用の発現割合は25%（All Grades）、Grade 3-5は6%であった。術後補助療法では新たな免疫関連の副作用は特定されなかった。

KEYTRUDA の化学療法との併用投与［用法・用量（4.2）参照］

KEYTRUDA を併用投与する際は、投与開始前に併用薬剤の各成分について添付文書を参照すること。

5183例の様々ながん種の患者を対象とした臨床試験で、KEYTRUDA（200 mg、2 mg/kg 又は10 mg/kg を3週間間隔）と化学療法との併用投与の安全性を評価した。高頻度に認められた有害事象は、貧血（52%）、悪心（52%）、疲労（35%）、下痢（33%）、便秘（32%）、嘔吐（28%）、食欲減退（28%）、好中球数減少（27%）、及び好中球減少症（25%）であった。Grade 3-5の有害事象の発現割合は、非小細胞肺癌患者に対する KEYTRUDA の併用投与で69%及び化学療法単独で61%、頭頸部扁平上皮癌患者に対する KEYTRUDA の併用投与で85%及び化学療法とセツキシマブの併用投与で84%、食道癌患者に対する KEYTRUDA の併用投与で86%及び化学療法単独で83%、トリプルネガティブ乳癌患者に対する KEYTRUDA の併用投与で80%及び化学療法単独で77%、子宮頸癌患者に対する KEYTRUDA の併用投与で82%及びベバシズマブ併用又は非併用の化学療法で75%、胃癌患者に対する KEYTRUDA の併用投与（トラスツズマブ併用又は非併用の化学療法）で74%、トラスツズマブ併用又は非併用の化学療法で68%、並びに胆道癌患者に対する KEYTRUDA の併用投与で85%及び化学療法単独で84%であった。

KEYTRUDA のチロシンキナーゼ阻害剤（TKI）との併用投与［用法・用量（4.2）参照］

KEYTRUDA をアキシチニブ又はレンバチニブと併用投与する際は、投与開始前にアキシチニブ又はレンバチニブの添付文書を参照すること。進行性腎細胞癌に関連するレンバチニブの追加の安全性情報は Kisplyx の添付文書を、進行子宮体癌に関連するレンバチニブの追加の安全性情報は Lenvima の添付文書を参照すること。肝酵素上昇に関連するアキシチニブの追加の安全性情報は［警告及び使用上の注意（4.4）］を参照すること。

進行性腎細胞癌患者に KEYTRUDA とアキシチニブ又はレンバチニブを併用投与した臨床試験、

及び進行子宮体癌患者に KEYTRUDA とレンバチニブを併用投与した臨床試験で計1456例を対象とし、KEYTRUDA（200 mg を3週間間隔）とアキシチニブ（5 mg を1日2回）又はレンバチニブ（20 mg を1日1回）のいずれかを適切に併用投与した際の安全性を評価した。高頻度に認められた有害事象は、下痢（58%）、高血圧（54%）、甲状腺機能低下症（46%）、疲労（41%）、食欲減退（40%）、悪心（40%）、関節痛（30%）、嘔吐（28%）、体重減少（28%）、発声障害（28%）、腹痛（28%）、蛋白尿（27%）、手掌・足底発赤知覚不全症候群（26%）、発疹（26%）、口内炎（25%）、便秘（25%）、筋骨格痛（23%）、頭痛（23%）、及び咳嗽（21%）であった。腎細胞癌患者の Grade 3-5の有害事象の発現割合は、KEYTRUDA とアキシチニブ又はレンバチニブの併用投与で80%、スニチニブ単独投与で71%であった。子宮体癌患者の Grade 3-5の有害事象の発現割合は、KEYTRUDA とレンバチニブの併用投与で89%、化学療法の単独投与で73%であった。

副作用の要約表

臨床試験及び市販後の使用において、KEYTRUDA の単独投与又は化学療法若しくは他の抗悪性腫瘍剤との併用投与を受けた患者で報告された副作用を[表 1.6.2-58]に示す。副作用は器官別大分類ごと及び発現割合別に示した。発現割合は、非常によくみられる（1/10以上）、よくみられる（1/100以上～1/10未満）、あまりみられない（1/1000以上～1/100未満）、まれ（1/10000以上～1/1000未満）、非常にまれ（1/10000未満）及び不明（現在までに得られている情報からは推測できない）に分類した。各発現割合の分類において、重篤度の高い順に副作用を示した。KEYTRUDA の単独投与又は併用化学療法の薬剤成分で発現する副作用は、（これらの薬剤を併用投与した臨床試験で報告されなかった副作用であっても）併用投与中に発現する可能性がある。KEYTRUDA を併用投与する際の追加の安全性情報は、併用薬剤の各成分について添付文書を参照すること。

表 1.6.2-58　　KEYTRUDA の投与を受けた患者で報告された副作用†

	単独投与	化学療法との併用投与	アキシチニブ又はレンバチニブとの併用投与
感染症および寄生虫症			
非常によくみられる			尿路感染
よくみられる	肺炎	肺炎	肺炎
血液およびリンパ系障害			
非常によくみられる	貧血	貧血、好中球減少症、血小板減少症	貧血
よくみられる	血小板減少症、好中球減少症、リンパ球減少症	発熱性好中球減少症、白血球減少症、リンパ球減少症	好中球減少症、血小板減少症、リンパ球減少症、白血球減少症
あまりみられない	白血球減少症、免疫性血小板減少症、好酸球増加症	好酸球増加症	好酸球増加症
まれ	血球食食性リンパ組織球症、溶血性貧血、赤芽球癆	溶血性貧血、免疫性血小板減少症	
免疫系障害			
よくみられる	注入に伴う反応*	注入に伴う反応*	注入に伴う反応*
あまりみられない	サルコイドーシス*		
まれ		サルコイドーシス	
不明	実質臓器移植拒絶反応		

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内分泌障害			
非常によくみられる	甲状腺機能低下症*	甲状腺機能低下症*	甲状腺機能低下症
よくみられる	甲状腺機能亢進症	副腎機能不全*、甲状腺炎*、甲状腺機能亢進症*	副腎機能不全*、甲状腺機能亢進症、甲状腺炎*
あまりみられない	副腎機能不全*、下垂体炎*、甲状腺炎*	下垂体炎*	下垂体炎*
まれ	副甲状腺機能低下症	副甲状腺機能低下症	副甲状腺機能低下症
代謝および栄養障害			
非常によくみられる	食欲減退	低カリウム血症、食欲減退	食欲減退
よくみられる	低ナトリウム血症、低カリウム血症、低カルシウム血症	低ナトリウム血症、低カルシウム血症	低ナトリウム血症、低カリウム血症、低カルシウム血症
あまりみられない	1型糖尿病*	1型糖尿病*	1型糖尿病*
精神障害			
非常によくみられる		不眠症	
よくみられる	不眠症		不眠症
神経系障害			
非常によくみられる	頭痛	末梢性ニューロパチー、頭痛	頭痛、味覚不全
よくみられる	浮動性めまい、末梢性ニューロパチー、嗜眠、味覚不全	浮動性めまい、味覚不全、嗜眠	浮動性めまい、末梢性ニューロパチー、嗜眠
あまりみられない	筋無力症候群*、てんかん	脳炎*、てんかん	筋無力症候群*、脳炎*
まれ	ギラン・バレー症候群*、脳炎*、脊髄炎*、視神経炎、髄膜炎（無菌性）*	筋無力症候群、ギラン・バレー症候群*、視神経炎	視神経炎
眼障害			
よくみられる	ドライアイ	ドライアイ	ドライアイ
あまりみられない	ぶどう膜炎*		ぶどう膜炎*
まれ	フォークト・小柳・原田症候群	ぶどう膜炎*	フォークト・小柳・原田症候群
心臓障害			
よくみられる	不整脈‡（心房細動を含む）	不整脈‡（心房細動を含む）	不整脈‡（心房細動を含む）
あまりみられない	心筋炎、心嚢液貯留、心膜炎	心筋炎*、心嚢液貯留、心膜炎	心筋炎、心嚢液貯留
血管障害			
非常によくみられる			高血圧
よくみられる	高血圧	高血圧	
あまりみられない		血管炎*	血管炎*
まれ	血管炎*		
呼吸器、胸郭および縦隔障害			
非常によくみられる	呼吸困難、咳嗽	呼吸困難、咳嗽	呼吸困難、咳嗽
よくみられる	肺臓炎*	肺臓炎*	肺臓炎*
胃腸障害			
非常によくみられる	下痢、腹痛*、悪心、嘔吐、便秘	下痢、嘔吐、悪心、腹痛*、便秘	下痢、腹痛*、悪心、嘔吐、便秘
よくみられる	大腸炎*、口内乾燥	大腸炎*、胃炎*、口内乾燥	大腸炎*、膵炎*、胃炎*、口内乾燥
あまりみられない	膵炎*、胃炎*、消化管潰瘍*	膵炎*、消化管潰瘍*	消化管潰瘍*
まれ	膵外分泌不全、小腸穿孔、セリアック病	膵外分泌不全、小腸穿孔、セリアック病	小腸穿孔

不明			膵外分泌不全、セリアック病
肝胆道系障害			
よくみられる	肝炎*	肝炎*	肝炎*
まれ	硬化性胆管炎	硬化性胆管炎*	
皮膚および皮下組織障害			
非常によくみられる	そう痒症*、発疹*	脱毛症、そう痒症*、発疹*	発疹*、そう痒症*
よくみられる	重度の皮膚反応*、紅斑、皮膚炎、皮膚乾燥、尋常性白斑*、湿疹、脱毛症、ざ瘡様皮膚炎	重度の皮膚反応*、紅斑、皮膚炎、皮膚乾燥、ざ瘡様皮膚炎、湿疹	重度の皮膚反応*、皮膚炎、皮膚乾燥、紅斑、ざ瘡様皮膚炎、脱毛症
あまりみられない	乾癬、苔癬様角化症*、丘疹、毛髪変色	乾癬、尋常性白斑*、丘疹	湿疹、苔癬様角化症*、乾癬、尋常性白斑*、丘疹、毛髪変色
まれ	スティーヴンス・ジョンソン症候群、結節性紅斑、中毒性表皮壊死融解症	スティーヴンス・ジョンソン症候群、苔癬様角化症*、結節性紅斑、毛髪変色	中毒性表皮壊死融解症、スティーヴンス・ジョンソン症候群
筋骨格系および結合組織障害			
非常によくみられる	筋骨格痛*、関節痛	筋骨格痛*、関節痛	関節痛、筋骨格痛*、筋炎*、四肢痛
よくみられる	筋炎*、四肢痛、関節炎*	筋炎*、四肢痛、関節炎*	関節炎*
あまりみられない	腱鞘炎*	腱鞘炎*	腱鞘炎*
まれ	シェーグレン症候群	シェーグレン症候群	シェーグレン症候群
腎および尿路障害			
よくみられる		急性腎障害	腎炎*
あまりみられない	腎炎*	腎炎*、非感染性膀胱炎	
まれ	非感染性膀胱炎		非感染性膀胱炎
一般・全身障害および投与部位の状態			
非常によくみられる	疲労、無力症、浮腫*、発熱	疲労、無力症、発熱	疲労、無力症、浮腫*、発熱
よくみられる	インフルエンザ様疾患、悪寒	浮腫*、インフルエンザ様疾患、悪寒	インフルエンザ様疾患、悪寒
臨床検査			
非常によくみられる		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	リパーゼ増加、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、血中クレアチニン増加
よくみられる	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、血中アルカリホスファターゼ増加、高カルシウム血症、血中ビリルビン増加、血中クレアチニン増加	血中ビリルビン増加、血中アルカリホスファターゼ増加、血中クレアチニン増加、高カルシウム血症	アミラーゼ増加、血中ビリルビン増加、血中アルカリホスファターゼ増加、高カルシウム血症
あまりみられない	アミラーゼ増加	アミラーゼ増加	

† [表 1.6.2-58]に示した副作用の発現割合は、完全に KEYTRUDA のみに起因するものではなく、原疾患又は他の併用薬も一因となった可能性がある。

‡ 徐脈性不整脈及び頻脈性不整脈を含む標準クエリに基づく。

* 下記の事象名は、単一の事象ではなく、医学的状態を示す関連した事象の集まりを示す。

- Infusion-related reaction（薬物過敏症、アナフィラキシー反応、アナフィラキシー様反応、過敏症、輸注関連過敏反応、サイトカイン放出症候群及び血清病）
- サルコイドーシス（皮膚サルコイドーシス及び肺サルコイドーシス）
- 甲状腺機能低下症（粘液水腫、免疫性甲状腺機能低下症及び自己免疫性甲状腺機能低下症）
- 副腎機能不全（アジソン病、急性副腎皮質機能不全及び続発性副腎皮質機能不全）
- 甲状腺炎（自己免疫性甲状腺炎、無痛性甲状腺炎、甲状腺障害、急性甲状腺炎及び免疫性甲状腺炎）
- 甲状腺機能亢進症（バセドウ病）
- 下垂体炎（下垂体機能低下症及びリンパ球性下垂体炎）

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- 1型糖尿病（糖尿病性ケトアシドーシス）
- 筋無力症候群（重症筋無力症及び重症筋無力症の増悪）
- 脳炎（自己免疫性脳炎及び非感染性脳炎）
- ギラン・バレー症候群（軸索型ニューロパチー及び脱髄性多発ニューロパチー）
- 脊髄炎（横断性脊髄炎を含む）
- 無菌性髄膜炎（髄膜炎及び非感染性髄膜炎）
- ぶどう膜炎（脈絡網膜炎、虹彩炎及び虹彩毛様体炎）
- 心筋炎（自己免疫性心筋炎）
- 血管炎（中枢神経系血管炎、大動脈炎及び巨細胞性動脈炎）
- 肺臓炎（間質性肺疾患、器質化肺炎、免疫性肺臓炎、免疫性肺疾患及び自己免疫性肺疾患）
- 腹痛（腹部不快感、上腹部痛及び下腹部痛）
- 大腸炎（顕微鏡的大腸炎、腸炎、出血性腸炎、自己免疫性大腸炎及び免疫性腸炎）
- 胃炎（びらん性胃炎及び出血性胃炎）
- 膵炎（自己免疫性膵炎、急性膵炎及び免疫性膵炎）
- 消化管潰瘍（胃潰瘍及び十二指腸潰瘍）
- 肝炎（自己免疫性肝炎、免疫性肝炎、薬物性肝障害及び急性肝炎）
- 硬化性胆管炎（免疫介在性胆管炎）
- そう痒症（蕁麻疹、丘疹状蕁麻疹及び陰部そう痒症）
- 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、小水疱性皮疹及び性器発疹）
- 重度の皮膚反応（剥脱性発疹、天疱瘡、並びにGrade 3以上の皮膚血管炎、水疱性皮膚炎、剥脱性皮膚炎、全身性剥脱性皮膚炎、多形紅斑、扁平苔癬、口腔扁平苔癬、類天疱瘡、そう痒症、陰部そう痒症、発疹、紅斑性皮疹、斑状丘疹状皮疹、そう痒性皮疹、膿疱性皮疹、皮膚壊死及び中毒性皮疹）
- 尋常性白斑（皮膚色素脱失、皮膚色素減少及び眼瞼色素減少）
- 苔癬様角化症（扁平苔癬及び硬化性苔癬）
- 筋骨格痛（筋骨格不快感、背部痛、筋骨格硬直、筋骨格系胸痛及び斜頚）
- 筋炎（筋肉痛、ミオパチー、壊死性筋炎、リウマチ性多発筋痛及び横紋筋融解症）
- 関節炎（関節腫脹、多発性関節炎、関節滲出液、自己免疫性関節炎及び免疫性関節炎）
- 腱鞘炎（腱炎、滑膜炎及び腱痛）
- 腎炎（自己免疫性腎炎、免疫性腎炎、尿細管間質性腎炎及び腎不全、急性腎不全、又は腎炎を伴う急性腎障害、ネフローゼ症候群、糸球体腎炎、膜性糸球体腎炎並びに急性糸球体腎炎）
- 浮腫（末梢性浮腫、全身性浮腫、水分過負荷、体液貯留、眼瞼浮腫及び口唇浮腫、顔面浮腫、限局性浮腫、並びに眼窩周囲浮腫）

特定の副作用の記述

以下の免疫関連の副作用に関するデータは、臨床試験でKEYTRUDAの4つの用量（2 mg/kgを3週間間隔、10 mg/kgを2週間間隔又は10 mg/kgを3週間間隔、200 mgを3週間間隔）の投与を受けた患者に基づいている［薬力学的特性（5.1）参照］。これらの副作用の管理についてのガイドラインは、［警告及び使用上の注意（4.4）］に示した。

免疫関連の副作用［警告及び使用上の注意（4.4）参照］

免疫関連の肺臓炎

KEYTRUDAの投与を受けた患者の324例（4.2%）に肺臓炎が発現した。このうち、Grade 2は143例（1.9%）、Grade 3は81例（1.1%）、Grade 4は19例（0.2%）、Grade 5は9例（0.1%）であった。肺臓炎発現までの期間の中央値は3.9ヵ月（範囲：2日～27.2ヵ月）であり、罹患期間の中央値は2.0ヵ月（範囲：1日～51.0+ヵ月）であった。胸部照射歴のある患者（8.1%）では、胸部照射歴のない患者（3.9%）と比較して肺臓炎の発現割合が高かった。肺臓炎による投与中止は131例（1.7%）であった。196例が回復した。そのうち6例は回復したが後遺症を認めた。

非小細胞肺癌患者では、230例（6.1%）に肺臓炎が発現した。このうち、Grade 2は103例（2.7%）、Grade 3は63例（1.7%）、Grade 4は17例（0.4%）、Grade 5は10例（0.3%）であった。胸部照射歴のある局所進行性又は転移性非小細胞肺癌患者の8.9%に肺臓炎が発現した。古典的ホジキンリンパ腫患者では、肺臓炎（All Grades）の発現割合は、KEYNOTE-087試験（210例）での5.2%からKEYNOTE-

204試験（148例）での10.8%であった。

免疫関連の大腸炎

KEYTRUDA の投与を受けた患者の158例（2.1%）に大腸炎が発現した。このうち、Grade 2は49例（0.6%）、Grade 3は82例（1.1%）、Grade 4は6例（0.1%）であった。大腸炎発現までの期間の中央値は4.3ヵ月（範囲：2日～24.3ヵ月）であり、罹患期間の中央値は1.1ヵ月（範囲：1日～45.2ヵ月）であった。大腸炎による投与中止は48例（0.6%）であった。132例が回復した。そのうち2例は回復したが後遺症を認めた。KEYTRUDA の単独投与を受けた結腸・直腸癌患者（153例）では、大腸炎の発現割合は6.5%（All Grades）であり、Grade 3は2.0%、Grade 4は1.3%であった。

免疫関連の肝炎

KEYTRUDA の投与を受けた患者の80例（1.0%）に肝炎が発現した。このうち、Grade 2は12例（0.2%）、Grade 3は55例（0.7%）、Grade 4は8例（0.1%）であった。肝炎発現までの期間の中央値は3.5ヵ月（範囲：8日～26.3ヵ月）であり、罹患期間の中央値は1.3ヵ月（範囲：1日～29.0+ヵ月）であった。肝炎による投与中止は37例（0.5%）であった。60例が回復した。

免疫関連の腎炎

KEYTRUDA の単独投与を受けた患者の37例（0.5%）に腎炎が発現した。このうち、Grade 2は11例（0.1%）、Grade 3は19例（0.2%）、Grade 4は2例（<0.1%）であった。腎炎発現までの期間の中央値は4.2ヵ月（範囲：12日～21.4ヵ月）であり、罹患期間の中央値は3.3ヵ月（範囲：6日～28.2+ヵ月）であった。腎炎による投与中止は17例（0.2%）であった。25例が回復した。そのうち5例は回復したが後遺症を認めた。KEYTRUDA とペメトレキセド及びプラチナ製剤化学療法との併用投与を受けた非扁平上皮非小細胞肺癌患者（488例）では、腎炎の発現割合は1.4%（All Grades）であり、Grade 3及び4の発現割合はそれぞれ0.8%及び0.4%であった。

免疫関連の内分泌障害

KEYTRUDA の投与を受けた患者の74例（1.0%）に副腎機能不全が発現した。このうち、Grade 2は34例（0.4%）、Grade 3は31例（0.4%）、Grade 4は4例（0.1%）であった。副腎機能不全発現までの期間の中央値は5.4ヵ月（範囲：1日～23.7ヵ月）であり、罹患期間の中央値は未到達（範囲：3日～40.1+ヵ月）であった。副腎機能不全による投与中止は13例（0.2%）であった。28例が回復した。そのうち11例は回復したが後遺症を認めた。

KEYTRUDA の投与を受けた患者の52例（0.7%）に下垂体炎が発現した。このうち、Grade 2は23例（0.3%）、Grade 3は24例（0.3%）、Grade 4は1例（<0.1%）であった。下垂体炎発現までの期間の中央値は5.9ヵ月（範囲：1日～17.7ヵ月）であり、罹患期間の中央値は3.6ヵ月（範囲：3日～48.1+ヵ月）であった。下垂体炎による投与中止は14例（0.2%）であった。23例が回復した。そのうち8例は回復したが後遺症を認めた。

KEYTRUDA の投与を受けた患者の394例（5.2%）に甲状腺機能亢進症が発現した。このうち、

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Grade 2は108例（1.4%）、Grade 3は9例（0.1%）であった。甲状腺機能亢進症発現までの期間の中央値は1.4ヵ月（範囲：1日～23.2ヵ月）であり、罹患期間の中央値は1.6ヵ月（範囲：4日～43.1+ヵ月）であった。甲状腺機能亢進症による投与中止は4例（0.1%）であった。326例（82.7%）が回復した。そのうち11例は回復したが後遺症を認めた。術後補助療法として KEYTRUDA の単独投与を受けた悪性黒色腫、非小細胞肺癌及び腎細胞癌患者（2060例）では、甲状腺機能亢進症の発現割合は11.0%であり、このうち大半が Grade 1又は2であった。

KEYTRUDA の投与を受けた患者の939例（12.3%）に甲状腺機能低下症が発現した。このうち Grade 2は687例（9.0%）、Grade 3は8例（0.1%）であった。甲状腺機能低下症発現までの期間の中央値は3.4ヵ月（範囲：1日～25.9ヵ月）であり、罹患期間の中央値は未到達（範囲：2日～63.0+ヵ月）であった。甲状腺機能低下症による投与中止は6例（0.1%）であった。216例（23.0%）が回復した。そのうち16例は回復したが後遺症を認めた。古典的ホジキンリンパ腫患者（389例）では、甲状腺機能低下症の発現割合は17%であり、いずれも Grade 1又は2であった。KEYTRUDA の単独投与を受けた頭頸部扁平上皮癌患者（909例）では、甲状腺機能低下症の発現割合は16.1%（All Grades）であり、Grade 3の発現割合は0.3%であった。KEYTRUDA とプラチナ製剤及び5-フルオロウラシル（5-FU）の化学療法との併用投与を受けた頭頸部扁平上皮癌患者（276例）では、甲状腺機能低下症の発現割合は15.2%であり、いずれも Grade 1又は2であった。KEYTRUDA とアキシチニブ又はレンバチニブの併用投与を受けた患者（1456例）では、甲状腺機能低下症の発現割合は46.2%（All Grades）であり、Grade 3又は4の発現割合は0.8%であった。術後補助療法として KEYTRUDA の単独投与を受けた悪性黒色腫、非小細胞肺癌及び腎細胞癌患者（2060例）では、甲状腺機能低下症の発現割合は18.5%であり、このうち大半が Grade 1又は2であった。

免疫関連の皮膚反応

KEYTRUDA の投与を受けた患者の130例（1.7%）に免疫関連の重度の皮膚反応が発現した。このうち、Grade 2は11例（0.1%）、Grade 3は103例（1.3%）、Grade 4は1例（<0.1%）、Grade 5は1例（<0.1%）であった。重度の皮膚反応発現までの期間の中央値は2.8ヵ月（範囲：2日～25.5ヵ月）であり、罹患期間の中央値は1.9ヵ月（範囲：1日～47.1+ヵ月）であった。重度の皮膚反応による中止例は18例（0.2%）であった。95例が回復した。そのうち2例は回復したが後遺症を認めた。

発現割合がまれであるが、死亡を含むスティーヴンス・ジョンソン症候群及び中毒性表皮壊死融解症が報告されている［用法・用量（4.2）及び警告及び使用上の注意（4.4）参照］。

古典的ホジキンリンパ腫における同種造血幹細胞移植に伴う合併症

KEYNOTE-013試験では、KEYTRUDA の投与後に同種造血幹細胞移植を受けた患者14例中6例で急性移植片対宿主病、1例で慢性移植片対宿主病が報告され、いずれも死亡に至らなかった。2例に肝中心静脈閉塞症が発現し、うち1例の患者が死亡した。1例に移植後生着症候群が発現した。

KEYNOTE-087試験では、KEYTRUDA の投与後に同種造血幹細胞移植を受けた患者32例中16例で急性移植片対宿主病、7例で慢性移植片対宿主病が報告され、うち2例の患者が死亡した。肝中

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心静脈閉塞症を発現した患者はいなかった。移植後生着症候群を発現した患者もいなかった。

KEYNOTE-204試験では、KEYTRUDA の投与後に同種造血幹細胞移植を受けた患者14例中8例で急性移植片対宿主病、3例で慢性移植片対宿主病が報告され、いずれも死亡に至らなかった。肝中心静脈閉塞症を発現した患者はいなかった。1例に移植後生着症候群が発現した。

腎細胞癌患者における KEYTRUDA とアキシチニブの併用投与による肝酵素の上昇

未治療の腎細胞癌患者を対象とした KEYTRUDA とアキシチニブの併用投与の臨床試験において、想定された発現割合よりも高い Grade 3及び4の ALT 増加（20%）及び AST 増加（13%）がみられた。ALT 増加の発現までの期間の中央値は2.3ヵ月（範囲：7日～19.8ヵ月）であった。基準値上限の3倍以上の ALT 増加がみられた患者（Grade 2-4、116例）のうち94%は、ALT が Grade 1以下に回復した。ALT 増加がみられた患者の59%が全身性副腎皮質ホルモン剤の投与を受けた。回復した患者のうち、92例（84%）は KEYTRUDA（3%）、アキシチニブ（31%）又はその両剤（50%）が再投与された。そのうち55%の患者では、基準値上限の3倍超の ALT 増加の再発はみられず、基準値上限の3倍超の ALT 増加の再発がみられたすべての患者が回復した。Grade 5の肝関連事象は認められなかった。

臨床検査値異常

KEYTRUDA の単独投与を受けた患者のうち、ベースラインから Grade 3又は4の臨床検査値異常の変動を認めた患者の割合は以下のとおりであった。リンパ球減少（9.4%）、ナトリウム減少（7.4%）、ヘモグロビン減少（5.8%）、リン酸塩減少（5.3%）、ブドウ糖増加（5.3%）、ALT 増加（3.3%）、AST 増加（3.1%）、アルカリホスファターゼ増加（2.6%）、カリウム減少（2.3%）、カリウム増加（2.1%）、好中球減少（1.9%）、血小板減少（1.8%）、カルシウム増加（1.8%）、ビリルビン増加（1.7%）、カルシウム減少（1.5%）、アルブミン減少（1.4%）、クレアチニン増加（1.3%）、ブドウ糖減少（1.2%）、白血球減少（0.8%）、マグネシウム増加（0.7%）、ナトリウム増加（0.5%）、ヘモグロビン増加（0.4%）及びマグネシウム減少（0.2%）。

KEYTRUDA と化学療法との併用投与を受けた患者のうち、ベースラインから Grade 3又は4の臨床検査値異常の変動を認めた患者の割合は以下のとおりであった。好中球減少（39.9%）、リンパ球減少（25.5%）、白血球減少（23.3%）、ヘモグロビン減少（20.8%）、血小板減少（13.7%）、ナトリウム減少（10.4%）、カリウム減少（7.7%）、リン酸塩減少（7.3%）、ALT 増加（5.7%）、ブドウ糖増加（5.5%）、AST 増加（5.3%）、ビリルビン増加（3.6%）、カルシウム減少（3.5%）、カリウム増加（3.4%）、クレアチニン増加（3.1%）、アルカリホスファターゼ増加（2.8%）、アルブミン減少（2.6%）、カルシウム増加（1.7%）、ブドウ糖減少（1.0%）、ナトリウム増加（0.5%）、及びヘモグロビン増加（0.1%）。

KEYTRUDA とアキシチニブ又はレンバチニブとの併用投与を受けた患者のうち、ベースラインから Grade 3又は4の臨床検査値異常の変動を認めた患者の割合は以下のとおりであった。リパーゼ増加（23.0%）（KEYTRUDA とアキシチニブとの併用投与を受けた患者では測定しなかった）、

リンパ球減少（12.0%）、ナトリウム減少（11.4%）、アミラーゼ増加（11.2%）、トリグリセリド増加（11.2%）、ALT 増加（10.4%）、AST 増加（8.9%）、ブドウ糖増加（7.8%）、リン酸塩減少（6.8%）、カリウム減少（6.1%）、カリウム増加（5.1%）、コレステロール増加（4.5%）、クレアチニン増加（4.4%）、ヘモグロビン減少（4.2%）、マグネシウム減少（4.0%）、好中球減少（3.5%）、アルカリホスファターゼ増加（3.1%）、血小板減少（3.0%）、ビリルビン増加（2.8%）、カルシウム減少（2.2%）、白血球減少（1.7%）、マグネシウム増加（1.6%）、プロトロンビン INR 増加（1.5%）、ブドウ糖減少（1.4%）、アルブミン減少（1.2%）、カルシウム増加（1.2%）、ナトリウム増加（0.4%）、ヘモグロビン増加（0.1%）。

免疫原性

臨床試験で2 mg/kg を3週間間隔、200 mg を3週間間隔、10 mg/kg を2週間間隔又は10 mg/kg を3週間間隔で単独投与された患者で、評価可能であった2034例のうち、本剤の投与によって抗薬物抗体陽性となった患者は36例（1.8%）であり、そのうち9例（0.4%）の患者は、KEYTRUDA に対する中和抗体を有していた。抗 KEYTRUDA 抗体又は中和抗体の生成に伴う薬物動態及び安全性プロファイルに明らかな変化は認められなかった。

小児

第Ⅰ／Ⅱ相臨床試験の KEYNOTE-051試験で、進行悪性黒色腫、リンパ腫、若しくは PD-L1陽性の進行、再発又は治療抵抗性固形がんを有する生後9ヵ月～17歳の小児患者161例に対して、KEYTRUDA 2 mg/kg を3週間間隔で単独投与した場合の安全性を評価した。古典的ホジキンリンパ腫集団（22例）には、11～17歳の患者が含まれた。小児患者における安全性プロファイルは成人患者と概して同様であった。高頻度に認められた（20%以上）有害事象は、発熱（33%）、嘔吐（30%）、頭痛（26%）、腹痛（22%）、貧血（21%）、咳嗽（21%）及び便秘（20%）であった。単独投与で報告された有害事象のほとんどは Grade 1又は2であった。76例（47.2%）に Grade 3-5の有害事象が発現し、5例（3.1%）に死亡に至った有害事象が発現した。治験担当医師による因果関係の評価にかかわらず、発現頻度はすべての報告された有害事象に基づいている。ⅡB、ⅡC 又はⅢ期の悪性黒色腫を有する青少年に対し、KEYTRUDA を補助療法として投与した際の長期安全性データは得られていない。

副作用の報告

医薬品のリスク／ベネフィットバランスの継続的なモニタリングを行うため、医薬品の承認後の副作用が疑われる事象の報告は重要である。副作用が疑われる場合、医療従事者は、副作用の報告システム（付録5）を通じて報告すること。

過量投与

4.9　過量投与

KEYTRUDA の過量投与に関する情報は得られていない。

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過量投与が認められた場合、副作用の徴候及び症状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。

C Confidential

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

KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

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

Indications and Usage (1)	06/2024
Dosage and Administration (2)	06/2024
Warnings and Precautions (5)	03/2024

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

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma. (1.1)
- for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection. (1.1)

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.2)
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. (1.2)
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic. (1.2, 2.1)
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. (1.2, 2.1)
- for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. (1.2)
- as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC. (1.2)

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. (1.3)
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. (1.3, 2.1)
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. (1.3)

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL. (1.4)
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy. (1.4)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. (1.5)
- Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Cancer

- in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer. (1.6)
- as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.6)
- as a single agent for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. (1.6)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. (1.7, 2.1)

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test. (1.8, 2.1)

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.[1] (1.9)
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. (1.9)

Esophageal Cancer

- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test. (1.10, 2.1)

Cervical Cancer

- in combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer. (1.11)
- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. (1.11, 2.1)
- as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. (1.11, 2.1)

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen. (1.12)

Biliary Tract Cancer (BTC)

- in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer. (1.13)

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. (1.14)

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC. (1.15)
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC. (1.15)
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. (1.15)

Endometrial Carcinoma

- in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma. (1.16)
- in combination with lenvatinib, for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.16, 2.1)
- as a single agent, for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.16, 2.1)

Tumor Mutational Burden-High (TMB-H) Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1] (1.17, 2.1)
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation. (1.18)

Triple-Negative Breast Cancer (TNBC)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. (1.19)
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test. (1.19, 2.1)

Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for Classical Hodgkin Lymphoma and Primary Mediastinal Large B-Cell Lymphoma in adults.[2] (1.20, 2.2)

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

[2] This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

- Melanoma: 200 mg every 3 weeks or 400 mg every 6 weeks; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- NSCLC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- HNSCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- cHL or PMBCL: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- Urothelial Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MSI-H or dMMR Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- MSI-H or dMMR CRC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Gastric Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Esophageal Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Cervical Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- HCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- BTC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MCC: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- RCC: 200 mg every 3 weeks or 400 mg every 6 weeks as a single agent in the adjuvant setting, or in the advanced setting with either:
  - axitinib 5 mg orally twice daily or
  - lenvatinib 20 mg orally once daily. (2.2)
- Endometrial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks
  - in combination with carboplatin and paclitaxel regardless of MMR or MSI status, or
  - in combination with lenvatinib 20 mg orally once daily for pMMR or not MSI-H tumors, or
  - as a single agent for MSI-H or dMMR tumors. (2.2)
- TMB-H Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- cSCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- TNBC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Administer KEYTRUDA as an intravenous infusion over 30 minutes after dilution. (2.4)
- See Full Prescribing Information for dosage modifications for adverse reactions and preparation and administration instructions. (2.3, 2.4)

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

- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial (3)

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

None. (4)

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

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

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

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

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism. (6.1)
- KEYTRUDA in combination with chemotherapy or chemoradiotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, and hypothyroidism. (6.1)
- KEYTRUDA in combination with chemotherapy and bevacizumab: peripheral neuropathy, alopecia, anemia, fatigue/asthenia, nausea, neutropenia, diarrhea, hypertension, thrombocytopenia, constipation, arthralgia, vomiting, urinary tract infection, rash, leukopenia, hypothyroidism, and decreased appetite. (6.1)
- KEYTRUDA in combination with axitinib: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (6.1)
- KEYTRUDA in combination with lenvatinib: hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, weight loss, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia, dysphonia, rash, hepatotoxicity, and acute kidney injury. (6.1)
- KEYTRUDA in combination with enfortumab vedotin: rash, peripheral neuropathy, fatigue, pruritus, diarrhea, alopecia, weight loss, decreased appetite, dry eye, nausea, constipation, dysgeusia, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 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: 06/2024

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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 Melanoma

KEYTRUDA® is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.

1.2 Non-Small Cell Lung Cancer

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations, and is:

- Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

KEYTRUDA is indicated for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

1.3 Head and Neck Squamous Cell Cancer

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

1.4 Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

1.5 Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy.

Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

1.6 Urothelial Cancer

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:

- who are not eligible for any platinum-containing chemotherapy, or
- who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.

1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.9 Gastric Cancer

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.9)]*. Continued approval of this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

1.10 Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.11 Cervical Cancer

KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.

KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)].*

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.12 Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

1.13 Biliary Tract Cancer

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

1.14 Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

1.15 Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC.

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions *[see Clinical Studies (14.15)]*.

1.16 Endometrial Carcinoma

KEYTRUDA, in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.

1.17 Tumor Mutational Burden-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.17)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

1.18 Cutaneous Squamous Cell Carcinoma

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

1.19 Triple-Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.20 Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks

KEYTRUDA is indicated for use at an additional recommended dosage of 400 mg every 6 weeks for classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma in adults *[see Indications and Usage (1.4, 1.5), Dosage and Administration (2.2)]*. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety *[see Clinical Pharmacology (12.2), Clinical Studies (14.20)]*. Continued approval for this dosage may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on FDA-approved tests for patient selection is available at: **http://www.fda.gov/CcompanionDiagnostics** .

Patient Selection for Single-Agent Treatment

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- Stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.
- metastatic NSCLC *[see Clinical Studies (14.2)]*.
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.3)]*.
- previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.10)]*.
- recurrent or metastatic cervical cancer with disease progression on or after chemotherapy *[see Clinical Studies (14.11)]*.

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.7, 14.8)]*.

For the TMB-H indication, select patients for treatment with KEYTRUDA as a single agent based on TMB-H status in tumor specimens *[see Clinical Studies (14.17)]*.

Because subclonal dMMR mutations and microsatellite instability may arise in high-grade gliomas during temozolomide therapy, it is recommended to test for TMB-H, MSI-H, and dMMR in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Additional Patient Selection Information for MSI-H or dMMR in Patients with non-CRC Solid Tumors

Due to discordance between local tests and FDA-approved tests, confirmation of MSI-H or dMMR status is recommended by an FDA-approved test in patients with MSI-H or dMMR solid tumors, if feasible. If unable to perform confirmatory MSI-H/dMMR testing, the presence of TMB ≥10 mut/Mb, as determined by an FDA-approved test, may be used to select patients for treatment *[see Clinical Studies (14.7)]*.

Patient Selection for Combination Therapy

For use of KEYTRUDA in combination with chemotherapy and trastuzumab, select patients based on the presence of positive PD-L1 expression (CPS ≥1) in locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma *[see Clinical Studies (14.9)].*

For use of KEYTRUDA in combination with chemotherapy, with or without bevacizumab, select patients based on the presence of positive PD-L1 expression in persistent, recurrent, or metastatic cervical cancer *[see Clinical Studies (14.11)].*

For the pMMR/not MSI-H advanced endometrial carcinoma indication, select patients for treatment with KEYTRUDA in combination with lenvatinib based on MSI or MMR status in tumor specimens *[see Clinical Studies (14.16)]*.

For use of KEYTRUDA in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression in locally recurrent unresectable or metastatic TNBC *[see Clinical Studies (14.19)]*.

Additional Patient Selection Information

- An FDA-approved test for the detection of not MSI-H is currently unavailable for the selection of patients with not MSI-H endometrial carcinoma for treatment with KEYTRUDA in combination with lenvatinib *[see Clinical Studies (14.16)]*.

2.2 Recommended Dosage

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Monotherapy		
Adult patients with unresectable or metastatic melanoma	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, MSI-H or dMMR Endometrial Carcinoma, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with high-risk BCG-unresponsive NMIBC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients with cHL, PMBCL, MSI-H or dMMR Cancer, MCC, or TMB-H Cancer	2 mg/kg every 3 weeks (up to a maximum of 200 mg)*	Until disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients (12 years and older) for adjuvant treatment of melanoma	2 mg/kg every 3 weeks (up to a maximum of 200 mg)*	Until disease recurrence, unacceptable toxicity, or up to 12 months
Combination Therapy†		

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Adult patients with resectable NSCLC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity
Adult patients with NSCLC, HNSCC, HER2-negative Gastric Cancer, Esophageal Cancer, or BTC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced or metastatic urothelial cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA after enfortumab vedotin when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with HER2-positive Gastric Cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to trastuzumab and chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with Cervical Cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with RCC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA in combination with axitinib 5 mg orally twice daily‡ or Administer KEYTRUDA in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with Endometrial Carcinoma	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to carboplatin and paclitaxel when given on the same day. or Administer KEYTRUDA in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with high-risk early-stage TNBC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent for up to

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
		27 weeks (9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity[§]
Adult patients with locally recurrent unresectable or metastatic TNBC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

* 30-minute intravenous infusion

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

‡ When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

§ Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.

2.3 Dose Modifications

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

Dosage modifications for KEYTRUDA for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy with axitinib, see Table 3.	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver‡	Baseline AST or 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 or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold†
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue

Adverse Reaction	Severity*	Dosage Modification
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
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

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

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

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

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

The following table represents dosage modifications that are different from those described above for KEYTRUDA or in the Full Prescribing Information for the drug administered in combination.

Table 3: Recommended Specific Dosage Modifications for Adverse Reactions for KEYTRUDA in Combination with Axitinib

Treatment	Adverse Reaction	Severity	Dosage Modification
KEYTRUDA in combination with axitinib	Liver enzyme elevations*	ALT or AST increases to at least 3 times but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both KEYTRUDA and axitinib until resolution to Grades 0 or 1†
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST ≥10 times ULN	Permanently discontinue both KEYTRUDA and axitinib

* Consider corticosteroid therapy

† Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal

Recommended Dose Modifications for Adverse Reactions for KEYTRUDA in Combination with Lenvatinib

When administering KEYTRUDA in combination with lenvatinib, modify the dosage of one or both drugs. Withhold or discontinue KEYTRUDA as shown in Table 2. Refer to lenvatinib prescribing information for additional dose modification information.

2.4 Preparation and Administration

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

- Dilute KEYTRUDA injection (solution) prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. **Mix diluted solution by gentle inversion.** Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solution

The product does not contain a preservative.
Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

Administration

- Administer diluted solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated adverse reactions.

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

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

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

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

Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) of patients and withholding of KEYTRUDA in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence of pneumonitis. Pneumonitis resolved in 59% of the 94 patients.

In clinical studies enrolling 389 adult patients with cHL who received KEYTRUDA as a single agent, pneumonitis occurred in 31 (8%) patients, including Grades 3-4 pneumonitis in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range: 2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 21 (5.4%) patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

In a clinical study enrolling 580 adult patients with resected NSCLC (KEYNOTE-091) who received KEYTRUDA as a single agent for adjuvant treatment, pneumonitis occurred in 41 (7%) patients, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of KEYTRUDA in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% had resolution.

Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) of patients and withholding of KEYTRUDA in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence of colitis. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) of patients and withholding of KEYTRUDA in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.

KEYTRUDA with Axitinib

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

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both KEYTRUDA and axitinib. All patients with a recurrence of ALT ≥3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypophysitis

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

Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 94% (16/17) of patients with hypophysitis; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) of patients and withholding of KEYTRUDA in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Thyroid Disorders

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

Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). No patients discontinued KEYTRUDA due to thyroiditis. KEYTRUDA was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). Hyperthyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (2) of patients and withholding of KEYTRUDA in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

The incidence of new or worsening hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.2%) hyperthyroidism.

Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). Hypothyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

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

Type 1 diabetes mellitus occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. Type 1 diabetes mellitus led to permanent discontinuation in <0.1% (1) of patients and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. All patients with Type 1 diabetes mellitus required long-term insulin therapy.

Immune-Mediated Nephritis with Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 89% (8/9) of patients with nephritis. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) of patients and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of nephritis. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 40% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of KEYTRUDA in 0.1% (2) of patients and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence of immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other PD-

1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

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

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

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica

Endocrine: Hypoparathyroidism

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

5.2 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.3)]*.

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone

In two randomized trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Advise women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to KEYTRUDA as a single agent in 2799 patients in three randomized, open-label, active-controlled trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA as a single agent in a randomized, placebo-controlled trial (KEYNOTE-091), which enrolled 580 patients with resected NSCLC, a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active-controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087) and one randomized, open-label, active-controlled trial (KEYNOTE-204), which enrolled 389 patients with cHL; in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE-426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

Melanoma

Ipilimumab-Naive Melanoma

The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in KEYNOTE-006. KEYNOTE-006 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 32% had an elevated lactate dehydrogenase (LDH) value at baseline; 65% had M1c stage disease; 9% with history of brain metastasis; and approximately 36% had been previously treated with systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both

KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). Tables 4 and 5 summarize selected adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-006.

Table 4: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006

Adverse Reaction	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition				
Decreased appetite	16	0.5	14	0.8
Nervous System				
Headache	14	0.2	14	0.8

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

Table 5: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

Laboratory Test†	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205.
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2% Grades 3-4).

Ipilimumab-Refractory Melanoma

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was investigated in KEYNOTE-002. KEYNOTE-002 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). In the KEYTRUDA 2 mg/kg arm, 36% of patients were exposed to KEYTRUDA for ≥6 months and 4% were exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89); 61% male; 98% White; 41% had an elevated LDH value at baseline; 83% had M1c stage disease; 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor); and 15% with history of brain metastasis.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). Tables 6 and 7 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-002.

Table 6: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002

Adverse Reaction	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal				
Cough	18	0	16	0
General				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Musculoskeletal and Connective Tissue				
Arthralgia	14	0.6	10	1.2

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm
† Chemotherapy: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin
‡ Graded per NCI CTCAE v4.0
§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 7: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

Laboratory Test†	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased alkaline phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Decreased bicarbonate	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; decreased bicarbonate: KEYTRUDA n=263 and chemotherapy n=123.
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

Adjuvant Treatment of Resected Stage IIB or IIC Melanoma

Among the 969 patients with Stage IIB or IIC melanoma enrolled in KEYNOTE-716 *[see Clinical Studies (14.1)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 9.9 months (range: 0 to 15.4 months). Patients with autoimmune disease or a medical condition that required

immunosuppression or mucosal or ocular melanoma were ineligible. Adverse reactions occurring in patients with Stage IIB or IIC melanoma were similar to those occurring in 1011 patients with Stage III melanoma from KEYNOTE-054 or the 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Adjuvant Treatment of Stage III Resected Melanoma

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-054, a randomized (1:1) double-blind trial in which 1019 patients with completely resected Stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks (n=509) or placebo (n=502) for up to one year *[see Clinical Studies (14.1)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Seventy-six percent of patients received KEYTRUDA for 6 months or longer.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had Stage IIIA, 46% had Stage IIIB, 18% had Stage IIIC (1-3 positive lymph nodes), and 20% had Stage IIIC (≥4 positive lymph nodes).

Two patients treated with KEYTRUDA died from causes other than disease progression; causes of death were drug reaction with eosinophilia and systemic symptoms and autoimmune myositis with respiratory failure. Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. Adverse reactions leading to permanent discontinuation occurred in 14% of patients receiving KEYTRUDA; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 19% of patients; the most common (≥1%) were diarrhea (2.4%), pneumonitis (2%), increased ALT (1.4%), arthralgia (1.4%), increased AST (1.4%), dyspnea (1%), and fatigue (1%). Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-054.

Table 8: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-054

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=509		Placebo n=502	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	28	1.2	26	1.2
Nausea	17	0.2	15	0
Skin and Subcutaneous Tissue				
Pruritus	19	0	12	0
Rash	13	0.2	9	0
Musculoskeletal and Connective Tissue				
Arthralgia	16	1.2	14	0
Endocrine				
Hypothyroidism	15	0	2.8	0
Hyperthyroidism	10	0.2	1.2	0
Respiratory, Thoracic and Mediastinal				
Cough	14	0	11	0
General				
Asthenia	11	0.2	8	0
Influenza like illness	11	0	8	0
Investigations				
Weight loss	11	0	8	0

* Adverse reactions occurring at same or higher incidence than in placebo arm

† Graded per NCI CTCAE v4.03

Table 9: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-054

Laboratory Test†	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Increased ALT	27	2.4	16	0.2
Increased AST	24	1.8	15	0.4
Hematology				
Lymphopenia	24	1	16	1.2

* Laboratory abnormalities occurring at same or higher incidence than placebo.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 503 to 507 patients) and placebo (range: 492 to 498 patients).
‡ Graded per NCI CTCAE v4.03

NSCLC

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.2)]*. A total of 607 patients received KEYTRUDA 200 mg, pemetrexed and platinum every 3 weeks for 4 cycles followed by KEYTRUDA and pemetrexed (n=405) or placebo, pemetrexed, and platinum every 3 weeks for 4 cycles followed by placebo and pemetrexed (n=202). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 7.2 months (range: 1 day to 20.1 months). Sixty percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. Seventy-two percent of patients received carboplatin.

The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 or older; 59% male; 94% White and 3% Asian; and 18% with history of brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%). Tables 10 and 11 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-189.

Table 10: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-189

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=405		Placebo Pemetrexed Platinum Chemotherapy n=202	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	3.5	52	3.5
Constipation	35	1.0	32	0.5
Diarrhea	31	5	21	3.0
Vomiting	24	3.7	23	3.0
General				
Fatigue†	56	12	58	6
Pyrexia	20	0.2	15	0
Metabolism and Nutrition				
Decreased appetite	28	1.5	30	0.5
Skin and Subcutaneous Tissue				
Rash‡	25	2.0	17	2.5
Respiratory, Thoracic and Mediastinal				
Cough	21	0	28	0
Dyspnea	21	3.7	26	5

* Graded per NCI CTCAE v4.03
† Includes asthenia and fatigue
‡ Includes genital rash, rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 11: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-189

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy		Placebo Pemetrexed Platinum Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Anemia	85	17	81	18
Lymphopenia	64	22	64	25
Neutropenia	48	20	41	19
Thrombocytopenia	30	12	29	8
Chemistry				
Hyperglycemia	63	9	60	7
Increased ALT	47	3.8	42	2.6
Increased AST	47	2.8	40	1.0
Hypoalbuminemia	39	2.8	39	1.1
Increased creatinine	37	4.2	25	1.0
Hyponatremia	32	7	23	6
Hypophosphatemia	30	10	28	14
Increased alkaline phosphatase	26	1.8	29	2.1
Hypocalcemia	24	2.8	17	0.5
Hyperkalemia	24	2.8	19	3.1
Hypokalemia	21	5	20	5

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/pemetrexed/platinum chemotherapy (range: 381 to 401 patients) and placebo/pemetrexed/platinum chemotherapy (range: 184 to 197 patients).
† Graded per NCI CTCAE v4.03

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy

The safety of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in 558 patients with previously untreated, metastatic squamous NSCLC *[see*

Clinical Studies (14.2)]. Safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA was 7 months (range: 1 day to 12 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. A total of 139 of 203 patients (68%) received paclitaxel and 64 patients (32%) received paclitaxel protein-bound in combination with carboplatin.

The study population characteristics were: median age of 65 years (range: 40 to 83), 52% age 65 or older; 78% male; 83% White; and 9% with history of brain metastases.

KEYTRUDA was discontinued for adverse reactions in 15% of patients, with no single type of adverse reaction accounting for the majority. Adverse reactions leading to interruption of KEYTRUDA occurred in 43% of patients; the most common (≥2%) were thrombocytopenia (20%), neutropenia (11%), anemia (6%), asthenia (2%), and diarrhea (2%). The most frequent (≥2%) serious adverse reactions were febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

The adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs. 36%) and peripheral neuropathy (31% vs. 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

Previously Untreated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated Stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC *[see Clinical Studies (14.2)].* Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator's choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA was 5.6 months (range: 1 day to 27.3 months). Forty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA 200 mg for ≥6 months.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Eighty-seven percent had metastatic disease (Stage IV), 13% had Stage III disease (2% Stage IIIA and 11% Stage IIIB), and 5% had treated brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 19% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3.0%), death due to unknown cause (1.6%), and pneumonia (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 33% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were pneumonitis (3.1%), pneumonia (3.0%), hypothyroidism (2.2%), and increased ALT (2.0%). The most frequent (≥2%) serious adverse reactions were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%).

Tables 12 and 13 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-042.

Table 12: Adverse Reactions Occurring in ≥10% of Patients in KEYNOTE-042

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=636		Chemotherapy n=615	
	All Grades* (%)	Grades 3-5 (%)	All Grades (%)	Grades 3-5 (%)
General				
Fatigue†	25	3.1	33	3.9
Pyrexia	10	0.3	8	0
Metabolism and Nutrition				
Decreased appetite	17	1.7	21	1.5
Respiratory, Thoracic and Mediastinal				
Dyspnea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Skin and Subcutaneous Tissue				
Rash‡	15	1.3	8	0.2
Gastrointestinal				
Constipation	12	0	21	0.2
Diarrhea	12	0.8	12	0.5
Nausea	12	0.5	32	1.1
Endocrine				
Hypothyroidism	12	0.2	1.5	0
Infections				
Pneumonia	12	7	9	6
Investigations				
Weight loss	10	0.9	7	0.2

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 13: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-042

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	4.7	51	5
Increased ALT	33	4.8	34	2.9
Hypoalbuminemia	33	2.2	29	1.0
Increased AST	31	3.6	32	1.7
Hyponatremia	31	9	32	8
Increased alkaline phosphatase	29	2.3	29	0.3
Hypocalcemia	25	2.5	19	0.7
Hyperkalemia	23	3.0	20	2.2
Increased prothrombin INR	21	2.0	15	2.9
Hematology				
Anemia	43	4.4	79	19
Lymphopenia	30	7	41	13

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 598 to 610 patients) and chemotherapy (range: 588 to 597 patients); increased prothrombin INR: KEYTRUDA n=203 and chemotherapy n=173.
† Graded per NCI CTCAE v4.03

Previously Treated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations *[see Clinical Studies (14.2)]*. A total of 991 patients received KEYTRUDA 2 mg/kg (n=339) or 10 mg/kg (n=343) every 3 weeks or docetaxel (n=309) at 75 mg/m^2 every 3 weeks. Patients with autoimmune disease, medical conditions that required systemic

corticosteroids or other immunosuppressive medication, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 3.5 months (range 1 day to 20.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 31% of patients exposed to KEYTRUDA for ≥6 months. In the KEYTRUDA 10 mg/kg arm, 34% of patients were exposed to KEYTRUDA for ≥6 months.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; and 8% with advanced localized disease, 91% with metastatic disease, and 15% with history of brain metastases. Twenty-nine percent received two or more prior systemic treatments for advanced or metastatic disease.

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for adverse reactions in 8% of patients receiving KEYTRUDA. The most common adverse events resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). Tables 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-010.

Table 14: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010

Adverse Reaction	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Metabolism and Nutrition				
Decreased appetite	25	1.5	23	2.6
Respiratory, Thoracic and Mediastinal				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
Gastrointestinal				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
Skin and Subcutaneous Tissue				
Rash‡	17	0.4	8	0
Pruritus	11	0	3	0.3
Musculoskeletal and Connective Tissue				
Arthralgia	11	1.0	9	0.3
Back pain	11	1.5	8	0.3

* Adverse reactions occurring at same or higher incidence than in docetaxel arm

† Graded per NCI CTCAE v4.0

‡ Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (25%), diarrhea (14%), asthenia (11%) and pyrexia (11%).

Table 15: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010

Laboratory Test†	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hyponatremia	32	8	27	2.9
Increased alkaline phosphatase	28	3.0	16	0.7
Increased AST	26	1.6	12	0.7
Increased ALT	22	2.7	9	0.4

* Laboratory abnormalities occurring at same or higher incidence than in docetaxel arm.

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 631 to 638 patients) and docetaxel (range: 274 to 277 patients).

‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were hyperglycemia (44% all Grades; 4.1% Grades 3-4), anemia (37% all Grades; 3.8% Grades 3-4), hypertriglyceridemia (36% all Grades; 1.8% Grades 3-4), lymphopenia (35% all Grades; 9% Grades 3-4), hypoalbuminemia (34% all Grades; 1.6% Grades 3-4), and hypercholesterolemia (20% all Grades; 0.7% Grades 3-4).

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

The safety of KEYTRUDA in combination with neoadjuvant platinum-containing chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent after surgery was investigated in KEYNOTE-671, a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition *[see Clinical Studies (14.2)].* Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 10.9 months (range: 1 day to 18.6 months). The study population characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older, 7% age 75 or older; 71% male; 61% White, 31% Asian, 2% Black, 4% race not reported; 9% Hispanic or Latino.

Adverse reactions occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum containing chemotherapy, given as neoadjuvant treatment and continued as single agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

Neoadjuvant Phase of KEYNOTE-671

A total of 396 patients received at least 1 dose of KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment and 399 patients received at least 1 dose of placebo in combination with platinum-containing chemotherapy as neoadjuvant treatment.

Serious adverse reactions occurred in 34% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%).

Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the 396 KEYTRUDA-treated patients and 399 placebo-treated patients who received neoadjuvant treatment, 6% (n=25) and 4.3% (n=17), respectively, did not receive surgery due to adverse reactions.

The most frequent (≥1%) adverse reactions that led to cancellation of surgery in the KEYTRUDA arm was interstitial lung disease (1%).

Of the 325 KEYTRUDA-treated patients who received surgery, 3.1% (n=10) experienced delay of surgery (surgery more than 8 weeks from last neoadjuvant treatment if patient received less than 4 cycles of neoadjuvant therapy or more than 20 weeks after first dose of neoadjuvant treatment if patient received 4 cycles of neoadjuvant therapy) due to adverse reactions. Of the 317 placebo-treated patients who received surgery, 2.5% (n=8) experienced delay of surgery due to adverse reactions.

Of the 325 KEYTRUDA-treated patients who received surgery, 7% (n=22) did not receive adjuvant treatment due to adverse reactions. Of the 317 placebo-treated patients who received surgery, 3.2% (n=10) did not receive adjuvant treatment due to adverse reactions.

Adjuvant Phase of KEYNOTE-671

A total of 290 patients in the KEYTRUDA arm and 267 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent KEYTRUDA as adjuvant treatment, 14% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of adjuvant KEYTRUDA due to an adverse reaction occurred in 12% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), AST increased (1%), and musculoskeletal pain (1%).

Adjuvant Treatment of Resected NSCLC

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-091, a multicenter, randomized (1:1), triple-blind, placebo-controlled trial in patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC; adjuvant chemotherapy up to 4 cycles was optional *[see Clinical Studies (14.2)]*. A total of 1161 patients received KEYTRUDA 200 mg (n=580) or placebo (n=581) every 3 weeks. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis.

The median duration of exposure to KEYTRUDA was 11.7 months (range: 1 day to 18.9 months). Sixty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months.

The adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

HNSCC

First-line treatment of metastatic or unresectable, recurrent HNSCC

The safety of KEYTRUDA, as a single agent and in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, was investigated in KEYNOTE-048, a multicenter, open-label, randomized (1:1:1), active-controlled trial in patients with previously untreated, recurrent or metastatic HNSCC *[see Clinical Studies (14.3)]*. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. A total of 576 patients received KEYTRUDA 200 mg every 3 weeks either as a single agent (n=300) or in combination with platinum and FU (n=276) every 3 weeks for 6 cycles followed by KEYTRUDA, compared to 287 patients who received cetuximab weekly in combination with platinum and FU every 3 weeks for 6 cycles followed by cetuximab.

The median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 24.2 months) in the KEYTRUDA single agent arm and was 5.8 months (range: 3 days to 24.2 months) in the combination arm. Seventeen percent of patients in the KEYTRUDA single agent arm and 18% of patients in the combination arm were exposed to KEYTRUDA for ≥12 months. Fifty-seven percent of patients receiving KEYTRUDA in combination with chemotherapy started treatment with carboplatin.

KEYTRUDA was discontinued for adverse reactions in 12% of patients in the KEYTRUDA single agent arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were sepsis (1.7%) and pneumonia (1.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 31% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were pneumonia (2.3%), pneumonitis (2.3%), and hyponatremia (2%).

KEYTRUDA was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 45% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 16: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-048

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=300		KEYTRUDA 200 mg every 3 weeks Platinum FU n=276		Cetuximab Platinum FU n=287	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General						
Fatigue[†]	33	4	49	11	48	8
Pyrexia	13	0.7	16	0.7	12	0
Mucosal inflammation	4.3	1.3	31	10	28	5
Gastrointestinal						
Constipation	20	0.3	37	0	33	1.4
Nausea	17	0	51	6	51	6
Diarrhea[‡]	16	0.7	29	3.3	35	3.1
Vomiting	11	0.3	32	3.6	28	2.8
Dysphagia	8	2.3	12	2.9	10	2.1
Stomatitis	3	0	26	8	28	3.5
Skin						
Rash[§]	20	2.3	17	0.7	70	8
Pruritus	11	0	8	0	10	0.3
Respiratory, Thoracic and Mediastinal						
Cough[¶]	18	0.3	22	0	15	0
Dyspnea[#]	14	2.0	10	1.8	8	1.0
Endocrine						
Hypothyroidism	18	0	15	0	6	0
Metabolism and Nutrition						
Decreased appetite	15	1.0	29	4.7	30	3.5
Weight loss	15	2	16	2.9	21	1.4
Infections						
Pneumonia[Þ]	12	7	19	11	13	6
Nervous System						
Headache	12	0.3	11	0.7	8	0.3
Dizziness	5	0.3	10	0.4	13	0.3
Peripheral sensory neuropathy[β]	1	0	14	1.1	7	1
Musculoskeletal						
Myalgia[a]	12	1.0	13	0.4	11	0.3
Neck pain	6	0.7	10	1.1	7	0.7
Psychiatric						
Insomnia	7	0.7	10	0	8	0

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

§ Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, seborrheic dermatitis

¶ Includes cough, productive cough

Includes dyspnea, exertional dyspnea

Þ Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal

β Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia

a Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

Table 17: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-048

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks Platinum FU		Cetuximab Platinum FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology						
Lymphopenia	54	25	69	35	74	45
Anemia	52	7	89	28	78	19
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	7	1.4	67	35	71	42
Chemistry						
Hyperglycemia	47	3.8	55	6	66	4.7
Hyponatremia	46	17	56	20	59	20
Hypoalbuminemia	44	3.2	47	4.0	49	1.1
Increased AST	28	3.1	24	2.0	37	3.6
Increased ALT	25	2.1	22	1.6	38	1.8
Increased alkaline phosphatase	25	2.1	27	1.2	33	1.1
Hypercalcemia	22	4.6	16	4.3	13	2.6
Hypocalcemia	22	1.1	32	4	58	7
Hyperkalemia	21	2.8	27	4.3	29	4.3
Hypophosphatemia	20	5	35	12	48	19
Hypokalemia	19	5	34	12	47	15
Increased creatinine	18	1.1	36	2.3	27	2.2
Hypomagnesemia	16	0.4	42	1.7	76	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/chemotherapy (range: 235 to 266 patients), KEYTRUDA (range: 241 to 288 patients), cetuximab/chemotherapy (range: 249 to 282 patients).

† Graded per NCI CTCAE v4.0

Previously treated recurrent or metastatic HNSCC

Among the 192 patients with HNSCC enrolled in KEYNOTE-012 *[see Clinical Studies (14.3)]*, the median duration of exposure to KEYTRUDA was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for KEYNOTE-012.

The study population characteristics were: median age of 60 years (range: 20 to 84), 35% age 65 or older; 83% male; and 77% White, 15% Asian, and 5% Black. Sixty-one percent of patients had two or more lines of therapy in the recurrent or metastatic setting, and 95% had prior radiation therapy. Baseline ECOG PS was 0 (30%) or 1 (70%) and 86% had M1 disease.

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); therefore, summary safety results are provided in a pooled analysis. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.1)]*.

Relapsed or Refractory cHL

KEYNOTE-204

The safety of KEYTRUDA was evaluated in KEYNOTE-204 *[see Clinical Studies (14.4)].* Adults with relapsed or refractory cHL received KEYTRUDA 200 mg intravenously every 3 weeks (n=148) or

brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks (n=152). The trial required an ANC ≥1000/µL, platelet count ≥75,000/µL, hepatic transaminases ≤2.5 times the upper limit of normal (ULN), bilirubin ≤1.5 times ULN, and ECOG performance status of 0 or 1. The trial excluded patients with active non-infectious pneumonitis, prior pneumonitis requiring steroids, active autoimmune disease, a medical condition requiring immunosuppression, or allogeneic HSCT within the past 5 years. The median duration of exposure to KEYTRUDA was 10 months (range: 1 day to 2.2 years), with 68% receiving at least 6 months of treatment and 48% receiving at least 1 year of treatment.

Serious adverse reactions occurred in 30% of patients who received KEYTRUDA. Serious adverse reactions in ≥1% included pneumonitis, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients (2%) died from causes other than disease progression: two from complications after allogeneic HSCT and one from unknown cause.

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 14% of patients; 7% of patients discontinued treatment due to pneumonitis. Dosage interruption of KEYTRUDA due to an adverse reaction occurred in 30% of patients. Adverse reactions which required dosage interruption in ≥3% of patients were upper respiratory tract infection, pneumonitis, transaminase increase, and pneumonia.

Thirty-eight percent of patients had an adverse reaction requiring systemic corticosteroid therapy.

Table 18 summarizes adverse reactions in KEYNOTE-204.

Table 18: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-204

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=148		Brentuximab Vedotin 1.8 mg/kg every 3 weeks N=152	
	All Grades* (%)	Grades 3- 4 (%)	All Grades* (%)	Grades 3- 4† (%)
Infections				
Upper respiratory tract infection‡	41	1.4	24	0
Urinary tract infection	11	0	3	0.7
Musculoskeletal and Connective Tissue				
Musculoskeletal pain§	32	0	29	1.3
Gastrointestinal				
Diarrhea¶	22	2.7	17	1.3
Nausea	14	0	24	0.7
Vomiting	14	1.4	20	0
Abdominal pain#	11	0.7	13	1.3
General				
Pyrexia	20	0.7	13	0.7
Fatigueᵖ	20	0	22	0.7
Skin and Subcutaneous Tissue				
Rashᵝ	20	0	19	0.7
Pruritus	18	0	12	0
Respiratory, Thoracic and Mediastinal				
Coughà	20	0.7	14	0.7
Pneumonitisè	11	5	3	1.3
Dyspneað	11	0.7	7	0.7
Endocrine				
Hypothyroidism	19	0	3	0
Nervous System				
Peripheral neuropathyø	11	0.7	43	7
Headacheý	11	0	11	0

* Graded per NCI CTCAE v4.0
† Adverse reactions in BV arm were Grade 3 only.
‡ Includes acute sinusitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, viral upper respiratory tract infection
§ Includes arthralgia, back pain, bone pain, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity
¶ Includes diarrhea, gastroenteritis, colitis, enterocolitis
# Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
ᵖ Includes fatigue, asthenia
ᵝ Includes dermatitis acneiform, dermatitis atopic, dermatitis allergic, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, eczema, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption
à Includes cough, productive cough
è Includes pneumonitis, interstitial lung disease
ð Includes dyspnea, dyspnea exertional, wheezing
ø Includes dysesthesia, hypoesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy
ý Includes headache, migraine, tension headache

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included herpes virus infection (9%), pneumonia (8%), oropharyngeal pain (8%), hyperthyroidism (5%), hypersensitivity (4.1%), infusion reactions (3.4%), altered mental state (2.7%), and in 1.4% each, uveitis, myocarditis, thyroiditis, febrile neutropenia, sepsis, and tumor flare.

Table 19 summarizes laboratory abnormalities in KEYNOTE-204.

Table 19: Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL in KEYNOTE-204

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks		Brentuximab Vedotin 1.8 mg/kg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	46	4.1	36	2.0
Increased AST	39	5	41	3.9
Increased ALT	34	6	45	5
Hypophosphatemia	31	5	18	2.7
Increased creatinine	28	3.4	14	2.6
Hypomagnesemia	25	0	12	0
Hyponatremia	24	4.1	20	3.3
Hypocalcemia	22	2.0	16	0
Increased alkaline phosphatase	21	2.1	22	2.6
Hyperbilirubinemia	16	2.0	9	1.3
Hypoalbuminemia	16	0.7	19	0.7
Hyperkalemia	15	1.4	8	0
Hematology				
Lymphopenia	35	9	32	13
Thrombocytopenia	34	10	26	5
Neutropenia	28	8	43	17
Anemia	24	5	33	8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 143 to 148 patients) and BV (range: 146 to 152 patients); hypomagnesemia: KEYTRUDA n=53 and BV n=50.

† Graded per NCI CTCAE v4.0

KEYNOTE-087

Among the 210 patients with cHL who received KEYTRUDA in KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). Serious adverse reactions occurred in 16% of patients who received KEYTRUDA. Serious adverse reactions that occurred in ≥1% of patients included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease (GVHD) and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 5% of patients and dosage interruption due to an adverse reaction occurred in 26%. Fifteen percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 20 and 21 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-087.

Table 20: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=210	
	All Grades* (%)	Grade 3 (%)
General		
Fatigue†	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal		
Cough‡	24	0.5
Dyspnea§	11	1.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain¶	21	1.0
Arthralgia	10	0.5
Gastrointestinal		
Diarrhea#	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue		
Rash Þ	20	0.5
Pruritus	11	0
Endocrine		
Hypothyroidism	14	0.5
Infections		
Upper respiratory tract infection	13	0
Nervous System		
Headache	11	0.5
Peripheral neuropathyβ	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrheic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), and myelitis and myocarditis (0.5% each).

Table 21: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hypertransaminasemia‡	34	2
Increased alkaline phosphatase	17	0
Increased creatinine	15	0.5
Hematology		
Anemia	30	6
Thrombocytopenia	27	4
Neutropenia	24	7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 208 to 209 patients)

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

Hyperbilirubinemia occurred in less than 15% of patients on KEYNOTE-087 (10% all Grades, 2.4% Grade 3-4).

PMBCL

Among the 53 patients with PMBCL who received KEYTRUDA in KEYNOTE-170 *[see Clinical Studies (14.5)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months). Serious adverse reactions occurred in 26% of patients. Serious adverse reactions that occurred in >2% of patients included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 8% of patients and dosage interruption due to an adverse reaction occurred in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-170.

Table 22: Adverse Reactions (≥10%) in Patients with PMBCL who Received KEYTRUDA in KEYNOTE-170

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=53	
	All Grades* (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue		
Musculoskeletal pain†	30	0
Infections		
Upper respiratory tract infection‡	28	0
General		
Pyrexia	28	0
Fatigue§	23	2
Respiratory, Thoracic and Mediastinal		
Cough¶	26	2
Dyspnea	21	11
Gastrointestinal		
Diarrhea#	13	2
Abdominal pain Þ	13	0
Nausea	11	0
Cardiac		
Arrhythmia β	11	4
Nervous System		
Headache	11	0

* Graded per NCI CTCAE v4.0

† Includes arthralgia, back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, bone pain, neck pain, non-cardiac chest pain

‡ Includes nasopharyngitis, pharyngitis, rhinorrhea, rhinitis, sinusitis, upper respiratory tract infection

§ Includes fatigue, asthenia

¶ Includes allergic cough, cough, productive cough

Includes diarrhea, gastroenteritis

Þ Includes abdominal pain, abdominal pain upper

β Includes atrial fibrillation, sinus tachycardia, supraventricular tachycardia, tachycardia

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), and thyroiditis, pericardial effusion, pneumonitis, arthritis and acute kidney injury (2% each).

Table 23: Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with PMBCL who Received KEYTRUDA in KEYNOTE-170

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	47	0
Leukopenia	35	9
Lymphopenia	32	18
Neutropenia	30	11
Chemistry		
Hyperglycemia	38	4
Hypophosphatemia	29	10
Hypertransaminasemia‡	27	4
Hypoglycemia	19	0
Increased alkaline phosphatase	17	0
Increased creatinine	17	0
Hypocalcemia	15	4
Hypokalemia	15	4

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 44 to 48 patients)

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

Urothelial Cancer

Patients with urothelial cancer in combination with enfortumab vedotin

The safety of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39 in patients with locally advanced or metastatic urothelial cancer *[see Clinical Studies (14.6)].* A total of 440 patients received KEYTRUDA 200 mg on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle compared to 433 patients who received gemcitabine on Days 1 and 8 and investigator's choice of cisplatin or carboplatin on Day 1 of each 21-day cycle. Among patients who received KEYTRUDA and enfortumab vedotin, the median duration of exposure to KEYTRUDA was 8.5 months (range: 9 days to 28.5 months).

Fatal adverse reactions occurred in 3.9% of patients treated with KEYTRUDA in combination with enfortumab vedotin including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin. Serious adverse reactions in ≥2% of patients receiving KEYTRUDA in combination with enfortumab vedotin were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Permanent discontinuation of KEYTRUDA occurred in 27% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA were pneumonitis/ILD (4.8%) and rash (3.4%).

Dose interruptions of KEYTRUDA occurred in 61% of patients. The most common adverse reactions (≥2%) resulting in interruption of KEYTRUDA were rash (17%), peripheral neuropathy (7%), COVID-19 (5%), diarrhea (4.3%), pneumonitis/ILD (3.6%), neutropenia (3.4%), fatigue (3%), alanine aminotransferase increased (2.7%), hyperglycemia (2.5%), pneumonia (2%), and pruritus (2%).

Tables 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-A39.

Table 24: Adverse Reactions ≥20% (All Grades) in Patients Treated with KEYTRUDA in Combination with Enfortumab Vedotin in KEYNOTE-A39

Adverse Reaction	KEYTRUDA in combination with Enfortumab Vedotin n=440		Chemotherapy n=433	
	All Grades* %	Grades 3-4 %	All Grades* %	Grades 3-4 %
Skin and subcutaneous tissue disorders				
Rash†	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
General disorders and administration site conditions				
Fatigue†	51	6	57	7
Nervous system disorders				
Peripheral neuropathy†	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Weight loss	33	3.6	9	0.2
Eye disorders				
Dry eye†	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

* Graded per NCI CTCAE v4.03

† Includes multiple terms

Clinically relevant adverse reactions (<20%) include pyrexia (18%), dry skin (17%), vomiting (12%), pneumonitis/ILD (10%), hypothyroidism (10%), blurred vision (6%), infusion site extravasation (2%), and myositis (0.5%).

Table 25: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-A39

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Enfortumab Vedotin		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased aspartate aminotransferase	75	4.6	39	3.3
Increased creatinine	71	3.2	68	2.6
Hyperglycemia	66	14	54	4.7
Increased alanine aminotransferase	59	5	49	3.3
Hyponatremia	46	13	47	13
Hypophosphatemia	44	9	36	9
Hypoalbuminemia	39	1.8	35	0.5
Hypokalemia	26	5	16	3.1
Hyperkalemia	24	1.4	36	4.0
Hypercalcemia	21	1.2	14	0.2
Hematology				
Lymphopenia	58	15	59	17
Anemia	53	7	89	33
Neutropenia	30	9	80	50

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 407 to 439 patients)

† Graded per NCI CTCAE v4.03

Cisplatin-ineligible patients with urothelial cancer in combination with enfortumab vedotin

The safety of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-869 in patients with locally advanced or metastatic urothelial cancer and who are not eligible for cisplatin-based chemotherapy *[see Clinical Studies (14.6)]*. A total of 121 patients received KEYTRUDA 200 mg on Day 1, and enfortumab vedotin 1.25 mg/kg on days 1 and 8 of each 21-day cycle. The median duration of exposure to KEYTRUDA was 6.9 months (range 1 day to 29.6 months).

Fatal adverse reactions occurred in 5% of patients treated with KEYTRUDA in combination with enfortumab vedotin, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis (0.8%).

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA and enfortumab vedotin. Serious adverse reactions in ≥2% of patients receiving KEYTRUDA in combination with enfortumab vedotin were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), hematuria (3.3%), pneumonia (3.3%), pneumonitis (3.3%), sepsis (3.3%), anemia (2.5%), diarrhea (2.5%), hypotension (2.5%), myasthenia gravis (2.5%), myositis (2.5%), and urinary retention (2.5%).

Permanent discontinuation of KEYTRUDA occurred in 32% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA were pneumonitis (5%), peripheral neuropathy (5%), rash (3.3%), and myasthenia gravis (2.5%).

Dose interruptions of KEYTRUDA occurred in 69% of patients. The most common adverse reactions (≥2%) resulting in interruption of KEYTRUDA were peripheral neuropathy (22%), rash (17%), neutropenia (7%), fatigue (6%), diarrhea (5%), lipase increased (5%), acute kidney injury (3.3%), ALT increased (2.5%), and COVID-19 (2.5%).

Tables 26 and 27 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-869.

Table 26: Adverse Reactions Occurring in ≥20% of Patients Treated with KEYTRUDA in Combination with Enfortumab Vedotin in KEYNOTE-869

Adverse Reaction	KEYTRUDA in combination with Enfortumab Vedotin n=121	
	All Grades* %	Grade 3-4 %
Skin and subcutaneous tissue disorders		
Rash†	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy‡	65	3.3
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Weight loss	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

* Graded per NCI CTCAE v4.03

† Includes: blister, conjunctivitis, dermatitis, dermatitis bullous, dermatitis exfoliative generalized, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin exfoliation, and stomatitis

‡ Includes: dysesthesia, hypoesthesia, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and gait disturbance

Clinically relevant adverse reactions (<20%) include vomiting (19.8%), fever (18%), hypothyroidism (11%), pneumonitis/ILD (10%), myositis (3.3%), myasthenia gravis (2.5%), and infusion site extravasation (0.8%).

Table 27: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-869

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Enfortumab Vedotin	
	All Grades† %	Grades 3-4 %
Chemistry		
Hyperglycemia	74	13
Increased aspartate aminotransferase	73	9
Increased creatinine	69	3.3
Hyponatremia	60	19
Increased alanine aminotransferase	60	7
Increased lipase	59	32
Hypoalbuminemia	59	4.2
Hypophosphatemia	51	15
Hypokalemia	35	8
Increased potassium	27	1.7
Increased calcium	27	4.2
Hematology		
Anemia	69	15
Lymphopenia	64	17
Neutropenia	32	12

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 114 to 121 patients)

† Graded per NCI CTCAE v4.03

Platinum-Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who had one or more comorbidities. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible *[see Clinical Studies (14.6)]*. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression.

The median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 15.8 months).

KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥40 mg oral prednisone equivalent.

Table 28 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 28: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=370	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	38	6
Pyrexia	11	0.5
Weight loss	10	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain‡	24	4.9
Arthralgia	10	1.1
Metabolism and Nutrition		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Gastrointestinal		
Constipation	21	1.1
Diarrhea§	20	2.4
Nausea	18	1.1
Abdominal pain¶	18	2.7
Elevated LFTs#	13	3.5
Vomiting	12	0
Skin and Subcutaneous Tissue		
Rashᵖ	21	0.5
Pruritus	19	0.3
Edema peripheralᵝ	14	1.1
Infections		
Urinary tract infection	19	9
Blood and Lymphatic System		
Anemia	17	7
Respiratory, Thoracic, and Mediastinal		
Cough	14	0
Dyspnea	11	0.5
Renal and Urinary		
Increased blood creatinine	11	1.1
Hematuria	13	3.0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
§ Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
¶ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
# Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests
ᵖ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized
ᵝ Includes edema peripheral, peripheral swelling

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.6)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible.

The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 29: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain§	32	3.0	27	2.0
Skin and Subcutaneous Tissue				
Pruritus	23	0	6	0.4
Rash¶	20	0.4	13	0.4
Gastrointestinal				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea#	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
Metabolism and Nutrition				
Decreased appetite	21	3.8	21	1.2
Infections				
Urinary tract infection	15	4.9	14	4.3
Respiratory, Thoracic and Mediastinal				
Cough Þ	15	0.4	9	0
Dyspnea ß	14	1.9	12	1.2
Renal and Urinary				
Hematuria à	12	2.3	8	1.6

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes asthenia, fatigue, malaise, lethargy
§ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
¶ Includes rash maculo-papular, rash, genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrheic keratosis, lichenoid keratosis
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes cough, productive cough
ß Includes dyspnea, dyspnea exertional, wheezing
à Includes blood urine present, hematuria, chromaturia

Table 30: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	8	60	7
Anemia	52	13	68	18
Lymphopenia	45	15	53	25
Hypoalbuminemia	43	1.7	50	3.8
Hyponatremia	37	9	47	13
Increased alkaline phosphatase	37	7	33	4.9
Increased creatinine	35	4.4	28	2.9
Hypophosphatemia	29	8	34	14
Increased AST	28	4.1	20	2.5
Hyperkalemia	28	0.8	27	6
Hypocalcemia	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0

BCG-unresponsive High-risk NMIBC

The safety of KEYTRUDA was investigated in KEYNOTE-057, a multicenter, open-label, single-arm trial that enrolled 148 patients with high-risk non-muscle invasive bladder cancer (NMIBC), 96 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumors. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

The median duration of exposure to KEYTRUDA was 4.3 months (range: 1 day to 25.6 months).

KEYTRUDA was discontinued due to adverse reactions in 11% of patients. The most common adverse (>1%) reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥2%) were diarrhea (4%) and urinary tract infection (2%). Serious adverse reactions occurred in 28% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). Tables 31 and 32 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

Table 31: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-057

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=148	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	29	0.7
Peripheral edema‡	11	0
Gastrointestinal		
Diarrhea§	24	2.0
Nausea	13	0
Constipation	12	0
Skin and Subcutaneous Tissue		
Rash¶	24	0.7
Pruritus	19	0.7
Musculoskeletal and Connective Tissue		
Musculoskeletal pain#	19	0
Arthralgia	14	1.4
Renal and Urinary		
Hematuria	19	1.4
Respiratory, Thoracic, and Mediastinal		
Cough Þ	19	0
Infections		
Urinary tract infection	12	2.0
Nasopharyngitis	10	0
Endocrine		
Hypothyroidism	11	0

* Graded per NCI CTCAE v4.03
† Includes asthenia, fatigue, malaise
‡ Includes edema peripheral, peripheral swelling
§ Includes diarrhea, gastroenteritis, colitis
¶ Includes rash maculo-papular, rash, rash erythematous, rash pruritic, rash pustular, erythema, eczema, eczema asteatotic, lichenoid keratosis, urticaria, dermatitis
# Includes back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, neck pain
Þ Includes cough, productive cough

Table 32: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of BCG-unresponsive NMIBC Patients Receiving KEYTRUDA in KEYNOTE-057

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	59	8
Increased ALT	25	3.4
Hyponatremia	24	7
Hypophosphatemia	24	6
Hypoalbuminemia	24	2.1
Hyperkalemia	23	1.4
Hypocalcemia	22	0.7
Increased AST	20	3.4
Increased creatinine	20	0.7
Hematology		
Anemia	35	1.4
Lymphopenia	29	1.6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 124 to 147 patients)
† Graded per NCI CTCAE v4.03

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The safety of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancer enrolled in KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 *[see Clinical Studies (14.7)].* The median duration of exposure to KEYTRUDA was 6.2 months (range: 1 day to 53.5 months). Adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

Among the 153 patients with MSI-H or dMMR CRC enrolled in KEYNOTE-177 *[see Clinical Studies (14.8)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 30.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma

The safety of KEYTRUDA was evaluated in 433 patients with HER2-positive gastric or GEJ cancer enrolled in KEYNOTE-811, which included 217 patients treated with KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=189) or FP (n=28) every 3 weeks, compared to 216 patients treated with placebo, trastuzumab, and CAPOX (n=187) or FP (n=29) every 3 weeks *[see Clinical Studies (14.9)]*.

The median duration of exposure to KEYTRUDA was 5.8 months (range: 1 day to 17.7 months).

The study population characteristics were: median age of 63 years (range: 19 to 84), 43% age 65 or older; 81% male; 58% White, 35% Asian, and 0.9% Black; 44% ECOG PS of 0 and 56% ECOG PS of 1.

KEYTRUDA and placebo were discontinued due to adverse reactions in 6% of patients in each arm. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 58% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (18%), thrombocytopenia (12%), diarrhea (6%), anemia (3.7%), hypokalemia (3.7%), fatigue/asthenia (3.2%), decreased appetite (3.2%), increased AST (2.8%), increased blood bilirubin (2.8%), pneumonia (2.8%), increased ALT (2.3%), and vomiting (2.3%).

In the KEYTRUDA arm versus placebo, there was a difference of ≥5% incidence between patients treated with KEYTRUDA versus standard of care for diarrhea (53% vs 44%) and nausea (49% vs 44%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of ≥5% incidence between patients treated with KEYTRUDA versus standard of care for increased ALT (34% vs 29%) and increased creatinine (20% vs 10%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma

The safety of KEYTRUDA was evaluated in 1572 patients with HER2-negative gastric or GEJ cancer enrolled in KEYNOTE-859, which included 785 patients treated with KEYTRUDA 200 mg and FP (n=106) or CAPOX (n=674) every 3 weeks, compared to 787 patients who received placebo and FP (n=107) or CAPOX (n=679) every 3 weeks *[see Clinical Studies (14.9)]*.

The median duration of exposure to KEYTRUDA was 6.2 months (range: 1 day to 33.7 months).

Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. Serious adverse reactions in >2% of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%). Fatal adverse reactions occurred in 8% of patients who received KEYTRUDA, including infection (2.3%) and thromboembolism (1.3%).

Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 15% of patients. Adverse reaction resulting in permanent discontinuation of KEYTRUDA in ≥1% were infections (1.8%) and diarrhea (1.0%).

Dosage interruptions of KEYTRUDA due to an adverse reaction occurred in 65% of patients. Adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhea (5.5%), fatigue (4.8%), infection (4.8%), anemia (4.5%), increased AST (4.3%), increased ALT (3.8%), increased blood bilirubin (3.3%), white blood cell count decreased (2.2%), nausea (2%), palmar-plantar erythrodysesthesia syndrome (2%), and vomiting (2%).

Tables 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-859.

Table 33: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=785		Placebo and FP or CAPOX n=787	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy†	47	5	48	6
Gastrointestinal				
Nausea	46	3.7	46	4.4
Diarrhea	36	6	32	5
Vomiting	34	5	27	5
Abdominal Pain‡	26	2.8	24	2.9
Constipation	22	0.5	21	0.8
General				
Fatigue§	40	8	39	9
Metabolism and Nutrition				
Decreased appetite	29	3.3	29	2.5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	25	3.1	22	1.8
Investigations				
Weight loss	20	2.8	19	2.7

* Graded per NCI CTCAE v4.03

† Includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy

‡ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, abdominal pain upper, epigastric discomfort, gastrointestinal pain

§ Includes asthenia, fatigue

Table 34: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX		Placebo and FP or CAPOX	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	65	15	69	13
Thrombocytopenia	64	12	62	10
Neutropenia	63	25	58	20
Leukopenia	59	7	56	6
Lymphopenia	57	20	51	16
Chemistry				
Increased AST	57	4.7	48	3.6
Hypoalbuminemia	55	4.1	52	2.9
Hyperglycemia	53	6	52	4.6
Hypocalcemia	49	3.6	45	3.3
Increased alkaline phosphatase	48	6	41	5
Hyponatremia	40	13	40	12
Increased ALT	40	4.2	29	2.9
Hypokalemia	35	10	27	9
Bilirubin increased	32	5	30	5
Hypophosphatemia	30	10	27	8
Hypomagnesemia	29	0.3	22	0.7
Increased creatinine	21	3.5	18	1.7
Hyperkalemia	20	3.7	18	2.9
Increased INR	20	1.4	22	0

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/FP or CAPOX (range: 210 to 766 patients) and placebo/FP or CAPOX (range: 190 to 762 patients)

† Graded per NCI CTCAE v4.03

Esophageal Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal Cancer/Gastroesophageal Junction

The safety of KEYTRUDA, in combination with cisplatin and FU chemotherapy was investigated in KEYNOTE-590, a multicenter, double-blind, randomized (1:1), placebo-controlled trial for the first-line treatment in patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.10)]*. A total of 740 patients received either KEYTRUDA 200 mg (n=370) or placebo (n=370) every 3 weeks for up to 35 cycles, both in combination with up to 6 cycles of cisplatin and up to 35 cycles of FU.

The median duration of exposure was 5.7 months (range: 1 day to 26 months) in the KEYTRUDA combination arm and 5.1 months (range: 3 days to 27 months) in the chemotherapy arm.

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 67% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

Tables 35 and 36 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

Table 35: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-590

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=370		Placebo Cisplatin FU n=370	
	All Grades* (%)	Grades 3-4† (%)	All Grades* (%)	Grades 3-4† (%)
Gastrointestinal				
Nausea	67	7	63	7
Constipation	40	0	40	0
Diarrhea	36	4.1	33	3
Vomiting	34	7	32	5
Stomatitis	27	6	26	3.8
General				
Fatigue‡	57	12	46	9
Metabolism and Nutrition				
Decreased appetite	44	4.1	38	5
Investigations				
Weight loss	24	3.0	24	5

* Graded per NCI CTCAE v4.03
† One fatal event of diarrhea was reported in each arm.
‡ Includes asthenia, fatigue

Table 36: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Esophageal Cancer Patients Receiving KEYTRUDA in KEYNOTE-590

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Cisplatin FU		Chemotherapy (Cisplatin and FU)	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	83	21	86	24
Neutropenia	74	43	71	41
Leukopenia	72	21	73	17
Lymphopenia	55	22	53	18
Thrombocytopenia	43	5	46	8
Chemistry				
Hyperglycemia	56	7	55	6
Hyponatremia	53	19	54	19
Hypoalbuminemia	52	2.8	52	2.3
Increased creatinine	45	2.5	42	2.5
Hypocalcemia	44	3.9	38	2
Hypophosphatemia	37	9	31	10
Hypokalemia	30	12	34	15
Increased alkaline phosphatase	29	1.9	29	1.7
Hyperkalemia	28	3.6	27	2.6
Increased AST	25	4.4	22	2.8
Increased ALT	23	3.6	18	1.7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/cisplatin/FU (range: 345 to 365 patients) and placebo/cisplatin/FU (range: 330 to 358 patients)
† Graded per NCI CTCAE v4.03

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 *[see Clinical Studies (14.10)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required

immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The safety of KEYTRUDA in combination with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18, a placebo-controlled, randomized (1:1), multicenter, double-blind trial including 594 patients with FIGO 2014 Stage III-IVA cervical cancer *[see Clinical Studies (14.11)]*. Two hundred ninety-two patients received KEYTRUDA in combination with chemoradiotherapy and 302 patients received placebo in combination with chemoradiotherapy.

The median duration of exposure to KEYTRUDA was 12.1 months (range: 1 day to 27 months).

Fatal adverse reactions occurred in 1.4% of patients receiving KEYTRUDA in combination with chemoradiotherapy, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage.

Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemoradiotherapy. Serious adverse reactions occurring in ≥1% of patients included urinary tract infection (2.7%), urosepsis (1.4%), and sepsis (1%).

KEYTRUDA was discontinued for adverse reactions in 7% of patients. The most common adverse reaction (≥1%) resulting in permanent discontinuation was diarrhea (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 43% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were anemia (8%), COVID-19 (6%), SARS-CoV-2 test positive (3.1%), decreased neutrophil count (2.7%), diarrhea (2.7%), urinary tract infection (2.7%), and increased ALT (2.4%).

Table 37 and Table 38 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-A18.

Table 37: Adverse Reactions Occurring in ≥10% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving KEYTRUDA in KEYNOTE-A18

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy n=292		Placebo with chemoradiotherapy n=302	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	0	61	2.3
Diarrhea	50	3.8	50	4.3
Vomiting	33	1	34	1.7
Constipation	18	0	18	0.7
Abdominal pain	12	0.7	12	1.7
Infections				
Urinary tract infection†	32	4.1	31	4.6
General				
Fatigue‡	26	1	27	1.3
Pyrexia	12	0.3	13	0
Endocrine				
Hypothyroidism§	20	0.7	5	0
Hyperthyroidism	11	0.3	2.6	0
Metabolism and Nutrition				
Decreased appetite	17	0.7	17	0.3
Investigations				
Weight loss	17	1.4	18	1

Renal and Urinary				
Dysuria	11	0.3	12	0
Skin and Subcutaneous Tissue Disorders				
Rash¶	11	0.7	7	0.3
Reproductive System				
Pelvic pain	10	1	13	1.3

* Graded per NCI CTCAE v5.0
† Includes urinary tract infection, urinary tract infection pseudomonal, pyelonephritis acute, cystitis, Escherichia urinary tract infection
‡ Includes fatigue, asthenia
§ Includes hypothyroidism, autoimmune hypothyroidism
¶ Includes erythema multiforme, dermatitis, drug eruption, eczema, rash, skin exfoliation, dermatitis bullous, rash maculo-papular, lichen planus, dyshidrotic eczema, dermatitis acneiform

Table 38: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving KEYTRUDA in KEYNOTE-A18

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy		Placebo with chemoradiotherapy	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	99	96	99	92
Leukopenia	96	46	94	49
Anemia	88	31	81	25
Neutropenia	75	32	74	33
Thrombocytopenia	65	8	61	6
Chemistry				
Hypomagnesemia	59	4.2	63	3.4
Hyponatremia	54	3.8	47	4
Increased AST	45	1	39	1.7
Increased ALT	44	2.1	44	1
Hypocalcemia	43	4.8	40	4.3
Hypokalemia	42	14	38	10
Increased creatinine	41	6	43	6
Hypoalbuminemia	37	0.7	35	1.7
Increased alkaline phosphatase	34	0.3	33	0.3

* Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA + chemoradiotherapy (range: 286 to 291 patients) and placebo + chemoradiotherapy (range: 298 to 300 patients)
† Graded per NCI CTCAE v5.0

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent *[see Clinical Studies (14.11)]*. A total of 616 patients, regardless of tumor PD-L1 expression, received KEYTRUDA 200 mg and chemotherapy with or without bevacizumab (n=307) every 3 weeks or placebo and chemotherapy with or without bevacizumab (n=309) every 3 weeks.

The median duration of exposure to KEYTRUDA was 9.9 months (range: 1 day to 26 months).

Fatal adverse reactions occurred in 4.6% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab, including 3 cases of hemorrhage, 2 cases of sepsis, 2 cases

due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection.

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab. Serious adverse reactions in ≥3% of patients included febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), acute kidney injury (3.3%), and sepsis (3.3%).

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA (≥1%) was colitis (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 66% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were thrombocytopenia (15%), neutropenia (14%), anemia (11%), increased ALT (6%), leukopenia (5%), fatigue/asthenia (4.2%), urinary tract infection (3.6%), increased AST (3.3%), pyrexia (3.3%), diarrhea (2.6%), acute kidney injury (2.6%), increased blood creatinine (2.6%), colitis (2.3%), decreased appetite (2%), and cough (2%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common (≥20%) adverse reactions were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea (41%), neutropenia (41%), diarrhea (39%), hypertension (35%), thrombocytopenia (35%), constipation (31%), arthralgia (31%), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

Table 39 and Table 40 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-826.

Table 39: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-826

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=307		Placebo and chemotherapy* with or without bevacizumab n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy‡	58	4.2	57	6
Skin and Subcutaneous Tissue				
Alopecia	56	0	58	0
Rash§	22	3.6	15	0.3
General				
Fatigue¶	47	7	46	6
Gastrointestinal				
Nausea	40	2	44	1.6
Diarrhea	36	2	30	2.6
Constipation	28	0.3	33	1
Vomiting	26	2.6	27	1.9
Musculoskeletal and Connective Tissue				
Arthralgia	27	0.7	26	1.3
Vascular				
Hypertension	24	9	23	11
Infections				
Urinary tract infection	24	9	26	8

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Graded per NCI CTCAE v4.0
‡ Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia
§ Includes rash, rash maculo-papular, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular
¶ Includes fatigue, asthenia

Table 40: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-826

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and chemotherapy† with or without bevacizumab n=307		Placebo and chemotherapy† with or without bevacizumab n=309	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades‡ (%)	Grades 3-4 (%)
Hematology				
Anemia	80	35	77	33
Leukopenia	76	27	69	19
Neutropenia	66	39	58	31
Lymphopenia	61	33	56	33
Thrombocytopenia	57	19	53	15
Chemistry				
Hyperglycemia	51	4.7	46	2.3
Hypoalbuminemia	46	1.3	38	5
Hyponatremia	40	14	38	11
Increased ALT	40	7	38	6
Increased AST	40	6	36	3.0
Increased alkaline phosphatase	38	3.4	40	2.3
Hypocalcemia	37	4.0	31	5
Increased creatinine	34	5	32	6
Hypokalemia	29	7	26	7
Hyperkalemia	23	3.7	27	4.7
Hypercalcemia	21	1.0	20	1.3

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA plus chemotherapy (range: 297 to 301 patients) and placebo plus chemotherapy (range: 299 to 302 patients)

† Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

‡ Graded per NCI CTCAE v4.0

Previously Treated Recurrent or Metastatic Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of KEYNOTE-158 *[see Clinical Studies (14.11)]*, the median duration of exposure to KEYTRUDA was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 41 and 42 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 41: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=98	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	43	5
Pain‡	22	2.0
Pyrexia	19	1.0
Edema peripheral§	15	2.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain¶	27	5
Gastrointestinal		
Diarrhea#	23	2.0
Abdominal painÞ	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhageß	19	5
Infections		
UTIà	18	6
Infection (except UTI)è	16	4.1
Skin and Subcutaneous Tissue		
Rashð	17	2.0
Endocrine		
Hypothyroidism	11	0
Nervous System		
Headache	11	2.0
Respiratory, Thoracic and Mediastinal		
Dyspnea	10	1.0

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

‡ Includes breast pain, cancer pain, dysesthesia, dysuria, ear pain, gingival pain, groin pain, lymph node pain, oropharyngeal pain, pain, pain of skin, pelvic pain, radicular pain, stoma site pain, toothache

§ Includes edema peripheral, peripheral swelling

¶ Includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, myositis, neck pain, non-cardiac chest pain, pain in extremity

Includes colitis, diarrhea, gastroenteritis

Þ Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper

ß Includes epistaxis, hematuria, hemoptysis, metrorrhagia, rectal hemorrhage, uterine hemorrhage, vaginal hemorrhage

à Includes bacterial pyelonephritis, pyelonephritis acute, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis

è Includes cellulitis, clostridium difficile infection, device-related infection, empyema, erysipelas, herpes virus infection, infected neoplasm, infection, influenza, lower respiratory tract congestion, lung infection, oral candidiasis, oral fungal infection, osteomyelitis, pseudomonas infection, respiratory tract infection, tooth abscess, upper respiratory tract infection, uterine abscess, vulvovaginal candidiasis

ð Includes dermatitis, drug eruption, eczema, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash generalized, rash maculo-papular

Table 42: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	54	24
Lymphopenia	47	9
Chemistry		
Hypoalbuminemia	44	5
Increased alkaline phosphatase	42	2.6
Hyponatremia	38	13
Hyperglycemia	38	1.3
Increased AST	34	3.9
Increased creatinine	32	5
Hypocalcemia	27	0
Increased ALT	21	3.9
Hypokalemia	20	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 76 to 79 patients)

† Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥10% of patients receiving KEYTRUDA were hypophosphatemia (19% all Grades; 6% Grades 3-4), increased INR (19% all Grades; 0% Grades 3-4), hypercalcemia (14% all Grades; 2.6% Grades 3-4), platelet count decreased (14% all Grades; 1.3% Grades 3-4), activated partial thromboplastin time prolonged (14% all Grades; 0% Grades 3-4), hypoglycemia (13% all Grades; 1.3% Grades 3-4), white blood cell decreased (13% all Grades; 2.6% Grades 3-4), and hyperkalemia (13% all Grades; 1.3% Grades 3-4).

HCC

Previously Treated HCC

The safety of KEYTRUDA was investigated in KEYNOTE-394, a multicenter, double-blind, randomized, placebo-controlled trial that enrolled patients with previously treated HCC. Patients were randomized (2:1) and received KEYTRUDA 200 mg (n=299) or placebo (n=153) intravenously every 3 weeks for up to 35 cycles *[see Clinical Studies (14.12)]*.

The median duration of exposure was 3.3 months (range: 1 day to 27.3 months) in the KEYTRUDA arm and 2.2 months (range: 1 day to 15.5 months) in the placebo arm. KEYTRUDA was discontinued due to adverse reactions in 13% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was ascites (2.3%). Adverse reactions leading to interruption of KEYTRUDA occurred in 26% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were increased blood bilirubin (9%), increased AST (5%), and increased ALT (2%).

Tables 43 and 44 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-394.

Table 43: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving KEYTRUDA in KEYNOTE-394

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=299		Placebo n=153	
	All Grades* (%)	Grades 3-5 (%)	All Grades* (%)	Grades 3-5 (%)
General				
Pyrexia	18	0.7	14	0
Skin and Subcutaneous Tissue				
Rash†	18	0.7	7	0
Pruritus	12	0	4	0
Gastrointestinal				
Diarrhea	16	1.7	9	0
Metabolism and Nutrition				
Decreased appetite	15	0.3	9	0
Infections				
Upper respiratory tract infection	11	1.0	7	0.7
Respiratory, Thoracic, and Mediastinal				
Cough	11	0	9	0
Endocrine				
Hypothyroidism	10	0	7	0

* Graded per NCI CTCAE v4.03

† Includes dermatitis, dermatitis allergic, dermatitis bullous, rash, rash erythematous, rash maculo-papular, rash pustular, and blister.

Table 44: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with HCC Receiving KEYTRUDA in KEYNOTE-394

Laboratory Test*	KEYTRUDA		Placebo	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased AST	54	14	44	12
Increased bilirubin	47	11	36	7
Increased ALT	47	7	32	4.6
Increased gamma-glutamyl transferase (GGT)	40	20	39	15
Hypoalbuminemia	40	0.7	20	0.7
Increased alkaline phosphatase	39	4.1	34	4
Hyperglycemia	36	3.3	26	1.4
Hyponatremia	36	11	28	5
Hypophosphatemia	30	6	17	4
Hypocalcemia	24	1.4	15	0.7
Hematology				
Lymphopenia	44	11	34	4.6
Anemia	36	7	30	3.3
Decreased platelets	32	4.7	29	2
Leukopenia	30	1.3	21	0.7
Neutropenia	25	4.4	21	2

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 223 to 297 patients) and placebo (range: 144 to 151 patients).

† Graded per NCI CTCAE v4.03

BTC

The safety of KEYTRUDA in combination with gemcitabine and cisplatin, was investigated in KEYNOTE-966, a multicenter, double-blind, randomized, placebo-controlled trial in patients with locally advanced unresectable or metastatic BTC who had not received prior systemic therapy in the advanced disease setting *[see Clinical Studies (14.13)]*. A total of 1063 patients received either KEYTRUDA 200 mg plus gemcitabine and cisplatin chemotherapy (n=529) or placebo plus gemcitabine and cisplatin chemotherapy (n=534) every 3 weeks.

The median duration of exposure to KEYTRUDA was 6 months (range: 1 day to 28 months).

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA (≥1%) was pneumonitis (1.3%).

Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In the KEYTRUDA plus chemotherapy versus placebo plus chemotherapy arms, there was a difference of ≥5% incidence in adverse reactions between patients treated with KEYTRUDA versus placebo for pyrexia (26% vs 20%), rash (21% vs 13%), pruritus (15% vs 10%), and hypothyroidism (9% vs. 2.6%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of ≥5% incidence in laboratory abnormalities between patients treated with KEYTRUDA plus chemotherapy versus placebo plus chemotherapy for decreased lymphocytes (69% vs 61%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

MCC

Among the 105 patients with MCC enrolled in KEYNOTE-017 and KEYNOTE-913 *[see Clinical Studies (14.14)]*, the median duration of exposure to KEYTRUDA was 6.3 months (range 1 day to 28 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included increased lipase (17%).

RCC

In combination with axitinib in the first-line treatment of advanced RCC (KEYNOTE-426)

The safety of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 *[see Clinical Studies (14.15)]*. Patients with medical conditions that required systemic corticosteroids or other immunosuppressive medications or had a history of severe autoimmune disease other than type 1 diabetes, vitiligo, Sjogren's syndrome, and hypothyroidism stable on hormone replacement were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks and axitinib 5 mg orally twice daily, or sunitinib 50 mg once daily for 4 weeks and then off treatment for 2 weeks. The median duration of exposure to the combination therapy of KEYTRUDA and axitinib was 10.4 months (range: 1 day to 21.2 months).

The study population characteristics were: median age of 62 years (range: 30 to 89), 40% age 65 or older; 71% male; 80% White; and 80% Karnofsky Performance Status (KPS) of 90-100 and 20% KPS of 70-80.

Fatal adverse reactions occurred in 3.3% of patients receiving KEYTRUDA in combination with axitinib. These included 3 cases of cardiac arrest, 2 cases of pulmonary embolism and 1 case each of cardiac failure, death due to unknown cause, myasthenia gravis, myocarditis, Fournier's gangrene, plasma cell myeloma, pleural effusion, pneumonitis, and respiratory failure.

Serious adverse reactions occurred in 40% of patients receiving KEYTRUDA in combination with axitinib. Serious adverse reactions in ≥1% of patients receiving KEYTRUDA in combination with axitinib included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%).

Permanent discontinuation due to an adverse reaction of either KEYTRUDA or axitinib occurred in 31% of patients; 13% KEYTRUDA only, 13% axitinib only, and 8% both drugs. The most common adverse reaction (>1%) resulting in permanent discontinuation of KEYTRUDA, axitinib, or the combination was hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of KEYTRUDA infusions due to infusion-related reactions, occurred in 76% of patients receiving

KEYTRUDA in combination with axitinib. This includes interruption of KEYTRUDA in 50% of patients. Axitinib was interrupted in 64% of patients and dose reduced in 22% of patients. The most common adverse reactions (>10%) resulting in interruption of KEYTRUDA were hepatotoxicity (14%) and diarrhea (11%), and the most common adverse reactions (>10%) resulting in either interruption or reduction of axitinib were hepatotoxicity (21%), diarrhea (19%), and hypertension (18%).

The most common adverse reactions (≥20%) in patients receiving KEYTRUDA and axitinib were diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.

Twenty-seven percent (27%) of patients treated with KEYTRUDA in combination with axitinib received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 45 and 46 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with KEYTRUDA and axitinib in KEYNOTE-426.

Table 45: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Axitinib n=429		Sunitinib n=425	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, enteritis, enterocolitis hemorrhagic

‡ Includes hypertension, blood pressure increased, hypertensive crisis, labile hypertension

§ Includes ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased

¶ Includes rash, butterfly rash, dermatitis, dermatitis acneform, dermatitis atopic, dermatitis bullous, dermatitis contact, exfoliative rash, genital rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, seborrheic dermatitis, skin discoloration, skin exfoliation, perineal rash

Table 46: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Hematology				
Lymphopenia	33	11	46	8
Anemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/axitinib (range: 342 to 425 patients) and sunitinib (range: 345 to 422 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

In combination with lenvatinib in the first-line treatment of advanced RCC (KEYNOTE-581)

The safety of KEYTRUDA was evaluated in KEYNOTE-581 *[see Clinical Studies (14.15)]*. Patients received KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=352), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of KEYTRUDA and lenvatinib was 17 months (range: 0.1 to 39).

Fatal adverse reactions occurred in 4.3% of patients treated with KEYTRUDA in combination with lenvatinib, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of either of KEYTRUDA, lenvatinib or both due to an adverse reaction occurred in 37% of patients receiving KEYTRUDA in combination with lenvatinib; 29% KEYTRUDA only, 26% lenvatinib only, and 13% both. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA, lenvatinib, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 78% of patients receiving KEYTRUDA in combination with lenvatinib. KEYTRUDA was interrupted in 55% of

patients and both drugs were interrupted in 39% of patients. The most common adverse reactions (≥3%) resulting in interruption of KEYTRUDA were diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%).

Fifteen percent (15%) of patients treated with KEYTRUDA in combination with lenvatinib received an oral prednisone equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 47 and 48 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in ≥20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 47: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with Lenvatinib N=352		Sunitinib 50 mg N=340	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue*	63	9	56	8
Gastrointestinal				
Diarrhea†	62	10	50	6
Stomatitis‡	43	2	43	2
Nausea	36	3	33	1
Abdominal pain§	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders¶	58	4	41	3
Endocrine				
Hypothyroidism#	57	1	32	0
Vascular				
Hypertensionᵇ	56	29	43	20
Hemorrhagic eventsß	27	5	26	4
Metabolism				
Decreased appetiteª	41	4	31	1
Skin and Subcutaneous Tissue				
Rashè	37	5	17	1
Palmar-plantar erythrodysesthesia syndromeð	29	4	38	4
Investigations				
Weight loss	30	8	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	30	0	4	0
Renal and Urinary				
Proteinuriaø	30	8	13	3
Acute kidney injuryý	21	5	16	2
Hepatobiliary				
Hepatotoxicity£	25	9	21	5
Nervous System				
Headache	23	1	16	1

* Includes asthenia, fatigue, lethargy, malaise

† Includes diarrhea, gastroenteritis

‡ Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis

§ Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, upper abdominal pain

¶ Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw

[#] Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism

[Þ] Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure

[ß] Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, upper gastrointestinal hemorrhage

[à] Includes decreased appetite, early satiety

[è] Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular

[ð] Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema

[ø] Includes hemoglobinuria, nephrotic syndrome, proteinuria

[ý] Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic

[£] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, gamma-glutamyltransferase increased

Clinically relevant adverse reactions (<20%) that occurred in patients receiving KEYTRUDA with lenvatinib were myocardial infarction (3%) and angina pectoris (1%).

Table 48: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with Lenvatinib		Sunitinib 50 mg	
	All Grades %†	Grade 3-4 %†	All Grades %†	Grade 3-4 %†
Chemistry				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased AST	58	7	57	3
Hyperglycemia	55	7	48	3
Increased ALT	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Decreased albumin	34	0.3	22	0
Increased alkaline phosphatase	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16

* With at least one Grade increase from baseline

† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA with lenvatinib (range: 343 to 349 patients) and sunitinib (range: 329 to 335 patients).

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed on rechallenge in 10 patients receiving both KEYTRUDA and lenvatinib (n=38) and was not observed on rechallenge with KEYTRUDA alone (n=3).

Adjuvant treatment of RCC

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-564, a randomized (1:1) double-blind placebo-controlled trial in which 984 patients who had undergone nephrectomy for RCC received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks (n=488) or placebo (n=496) for up to one year *[see Clinical Studies (14.15)]*. The median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 14.3 months). Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Serious adverse reactions occurred in 20% of these patients receiving KEYTRUDA. Serious adverse reactions (≥1%) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% of those treated with KEYTRUDA, including one case of pneumonia.

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 21% of patients; the most common (≥1%) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 26% of patients; the most common (≥1%) were increased AST (2.3%), arthralgia (1.6%), hypothyroidism (1.6%), diarrhea (1.4%),

increased ALT (1.4%), fatigue (1.4%), rash, decreased appetite, and vomiting (1% each). Tables 49 and 50 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-564.

Table 49: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-564

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=488		Placebo n=496	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue				
Musculoskeletal pain‡	41	1.2	36	0.6
General				
Fatigue§	40	1.2	31	0.2
Skin and Subcutaneous Tissue				
Rash¶	30	1.4	15	0.4
Pruritus	23	0.2	13	0
Gastrointestinal				
Diarrhea#	27	2.7	23	0.2
Nausea	16	0.4	10	0
Abdominal painÞ	11	0.4	13	0.2
Endocrine				
Hypothyroidism	21	0.2	3.6	0
Hyperthyroidism	12	0.2	0.2	0
Respiratory, Thoracic and Mediastinal				
Coughß	17	0	12	0
Nervous System				
Headacheà	15	0.2	13	0
Hepatobiliary				
Hepatotoxicityè	14	3.7	7	0.6
Renal and Urinary				
Acute kidney injuryð	13	1.2	10	0.2

* Adverse reactions occurring at same or higher incidence than in placebo arm

† Graded per NCI CTCAE v4.0

‡ Includes arthralgia, back pain, myalgia, arthritis, pain in extremity, neck pain, musculoskeletal pain, musculoskeletal stiffness, spinal pain, musculoskeletal chest pain, bone pain, musculoskeletal discomfort

§ Includes asthenia, fatigue

¶ Includes rash, rash maculo-papular, rash papular, skin exfoliation, lichen planus, rash erythematous, eczema, rash macular, dermatitis acneiform, dermatitis, rash pruritic, Stevens-Johnson Syndrome, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome

\# Includes diarrhea, colitis, enterocolitis, frequent bowel movements, enteritis

Þ Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, gastrointestinal pain

ß Includes upper-airway cough syndrome, productive cough, cough

à Includes tension headache, headache, sinus headache, migraine with aura

è Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, transaminases increased, gamma-glutamyltransferase increased, bilirubin conjugated increased

ð Includes acute kidney injury, blood creatinine increased, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, nephropathy toxic

Table 50: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-564

Laboratory Test†	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Increased glucose	48	8	45	4.5
Increased creatinine	40	1.1	28	0.2
Increased INR	27	0.9	20	0.8
Hyponatremia	21	3.3	13	1.9
Increased ALT	20	3.8	11	0.2
Hematology				
Anemia	28	0.5	20	0.4

* Laboratory abnormalities occurring at same or higher incidence than placebo

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 440 to 449 patients) and placebo (range: 461 to 469 patients); increased INR: KEYTRUDA n=228 and placebo n=254.

‡ Graded per NCI CTCAE v4.03

Endometrial Carcinoma

Primary Advanced or Recurrent Endometrial Carcinoma

The safety of KEYTRUDA in combination with chemotherapy (paclitaxel and carboplatin) was investigated in KEYNOTE-868, a randomized (1:1), multicenter, double-blind, placebo-controlled trial that enrolled patients with advanced or recurrent endometrial carcinoma *[see Clinical Studies (14.16)]*. A total of 759 patients received KEYTRUDA 200 mg every 3 weeks and chemotherapy for 6 cycles followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles (n=382) or placebo and chemotherapy for 6 cycles followed by placebo for up to 14 cycles (n=377). The median duration of exposure to KEYTRUDA was 5.6 months (range: 1 day to 24.0 months).

Serious adverse reactions occurred in 35% of patients receiving KEYTRUDA in combination with chemotherapy, compared to 19% of patients receiving placebo in combination with chemotherapy.

Fatal adverse reactions occurred in 1.6% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 (0.5%), and cardiac arrest (0.3%).

KEYTRUDA was discontinued for an adverse reaction in 14% of patients. Chemotherapy dose reduction was required in 29% of patients receiving KEYTRUDA in combination with chemotherapy, compared to 23% of patients receiving placebo in combination with chemotherapy. There were no clinically meaningful differences in chemotherapy discontinuations or interruptions between arms.

Adverse reactions occurring in patients treated with KEYTRUDA and chemotherapy were generally similar to those observed with KEYTRUDA alone or chemotherapy alone with the exception of rash (33% all Grades; 2.9% Grades 3-4).

In Combination with Lenvatinib for the Treatment of Advanced Endometrial Carcinoma That Is pMMR or Not MSI-H.

The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings *[see Clinical Studies (14.16)]*. Patients with endometrial carcinoma that is pMMR or not MSI-H received KEYTRUDA 200 mg every 3 weeks in combination with lenvatinib 20mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

For patients with pMMR or not MSI-H tumor status, the median duration of study treatment was 7.2 months (range 1 day to 26.8 months) and the median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day to 25.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with KEYTRUDA and lenvatinib, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions (≥3%) were hypertension (4.4%) and urinary tract infections (3.2%).

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of KEYTRUDA (≥1%) was increased ALT (1.2%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 48% of these patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥3%) were diarrhea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Tables 51 and 52 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib in KEYNOTE-775.

Table 51: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-775

Adverse Reaction	Endometrial Carcinoma (pMMR or not MSI-H)			
	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=342		Doxorubicin or Paclitaxel n=325	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism†	67	0.9	0.9	0
Vascular				
Hypertension‡	67	39	6	2.5
Hemorrhagic events§	25	2.6	15	0.9
General				
Fatigue¶	58	11	54	6
Gastrointestinal				
Diarrhea#	55	8	20	2.8
Nausea	49	2.9	47	1.5
Vomiting	37	2.3	21	2.2
Stomatitisᵇ	35	2.6	26	1.2
Abdominal painß	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disordersâ	53	5	27	0.6
Metabolism				
Decreased appetiteê	44	7	21	0
Investigations				
Weight loss	34	10	6	0.3
Renal and Urinary				
Proteinuriaô	29	6	3.4	0.3
Infections				
Urinary tract infectionø	31	5	13	1.2
Nervous System				
Headache	26	0.6	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	22	0	0.6	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesiaÿ	23	2.9	0.9	0
Rash£	20	2.3	4.9	0

* Graded per NCI CTCAE v4.03

† Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, secondary hypothyroidism

‡ Includes hypertension, blood pressure increased, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, blood pressure fluctuation

§ Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, melena, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, vessel puncture site bruise

¶ Includes fatigue, asthenia, malaise, lethargy

Includes diarrhea, gastroenteritis

Þ Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration

ß Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort

à Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw

è Includes decreased appetite, early satiety

ð Includes proteinuria, protein urine present, hemoglobinuria

ø Includes urinary tract infection, cystitis, pyelonephritis

ý Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema

£ Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, application site rash

Table 52: Laboratory Abnormalities Worsened from Baseline* Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-775

	Endometrial Carcinoma (pMMR or not MSI-H)			
Laboratory Test†	KEYTRUDA 200 mg every 3 weeks and Lenvatinib		Doxorubicin or Paclitaxel	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %

Chemistry				
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased aspartate aminotransferase	58	9	23	1.6
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	53	6	32	3.8
Increased alanine aminotransferase	55	9	21	1.2
Hypercholesteremia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased alkaline phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.9
Increased lipase	36	14	13	3.9
Increased creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased amylase	25	7	8	1
Hyperkalemia	23	2.4	12	1.2
Increased creatine kinase	19	3.7	7	0
Increased bilirubin	18	3.6	6	1.6
Hematology				
Lymphopenia	50	16	65	20
Thrombocytopenia	50	8	30	4.7
Anemia	49	8	84	14
Leukopenia	43	3.5	83	43
Neutropenia	31	6	76	58

* With at least one grade increase from baseline

† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA and lenvatinib (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients).

‡ Graded per NCI CTCAE v4.03

As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

Among the 90 patients with MSI-H or dMMR endometrial carcinoma enrolled in KEYNOTE-158 *[see Clinical Studies (14.16)]* treated with KEYTRUDA as a single agent, the median duration of exposure to KEYTRUDA was 8.3 months (range: 1 day to 26.9 months). Adverse reactions occurring in patients with endometrial carcinoma were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

TMB-H Cancer

The safety of KEYTRUDA was investigated in 105 patients with TMB-H cancer enrolled in KEYNOTE-158 *[see Clinical Studies (14.17)].* The median duration of exposure to KEYTRUDA was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

cSCC

Among the 159 patients with advanced cSCC (recurrent or metastatic or locally advanced disease) enrolled in KEYNOTE-629 *[see Clinical Studies (14.18)]*, the median duration of exposure to KEYTRUDA was 6.9 months (range 1 day to 28.9 months). Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. Adverse reactions occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included lymphopenia (10%) and decreased sodium (10%).

TNBC

Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The safety of KEYTRUDA in combination with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522, a randomized (2:1), multicenter, double-blind, placebo-controlled trial in patients with newly diagnosed, previously untreated, high-risk early-stage TNBC.

A total of 778 patients on the KEYTRUDA arm received at least 1 dose of KEYTRUDA in combination with neoadjuvant chemotherapy followed by KEYTRUDA as adjuvant treatment after surgery, compared to 389 patients who received at least 1 dose of placebo in combination with neoadjuvant chemotherapy followed by placebo as adjuvant treatment after surgery *[see Clinical Studies (14.19)].*

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 13.3 months (range: 1 day to 21.9 months).

Fatal adverse reactions occurred in 0.9% of patients receiving KEYTRUDA, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction.

Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA. Serious adverse reactions in ≥2% of patients who received KEYTRUDA included febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%).

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions (≥1%) resulting in permanent discontinuation of KEYTRUDA were increased ALT (2.7%), increased AST (1.5%), and rash (1%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 57% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (26%), thrombocytopenia (6%), increased ALT (6%), increased AST (3.7%), anemia (3.5%), rash (3.2%), febrile neutropenia (2.8%), leukopenia (2.8%), upper respiratory tract infection (2.6%), pyrexia (2.2%), and fatigue (2.1%).

Tables 53 and 54 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-522.

Table 53: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with chemotherapy*/KEYTRUDA n=778		Placebo with chemotherapy*/Placebo n=389	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	70	8	66	3.9
Pyrexia	28	1.3	19	0.3
Gastrointestinal				
Nausea	67	3.7	66	1.8
Constipation	42	0	39	0.3
Diarrhea	41	3.2	34	1.8
Stomatitis§	34	2.7	29	1
Vomiting	31	2.7	28	1.5
Abdominal pain¶	24	0.5	23	0.8
Skin and Subcutaneous Tissue				
Alopecia	61	0	58	0
Rash#	52	5	41	0.5
Nervous System				
Peripheral neuropathyÞ	41	3.3	42	2.3
Headache	30	0.5	29	1
Musculoskeletal and Connective Tissue				
Arthralgia	29	0.5	31	0.3
Myalgia	20	0.5	19	0
Respiratory, Thoracic and Mediastinal				
Coughß	26	0.1	24	0
Metabolism and Nutrition				
Decreased appetite	23	0.9	17	0.3
Psychiatric				
Insomnia	21	0.5	19	0

* Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide
† Graded per NCI CTCAE v4.0
‡ Includes asthenia, fatigue
§ Includes aphthous ulcer, cheilitis, lip pain, lip ulceration, mouth ulceration, mucosal inflammation, oral mucosal eruption, oral pain, stomatitis, tongue blistering, tongue ulceration
¶ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
# Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, incision site rash, injection site rash, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash rubelliform, skin exfoliation, skin toxicity, toxic skin eruption, urticaria, vasculitic rash, viral rash
Þ Includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy
ß Includes cough, productive cough, upper-airway cough syndrome

Table 54: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy†/KEYTRUDA		Placebo with chemotherapy†/Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Hematology				
Anemia	97	22	96	19
Leukopenia	93	41	91	32
Neutropenia	88	62	89	62
Lymphopenia	80	28	74	22
Thrombocytopenia	58	11	57	9
Chemistry				
Increased ALT	71	9	69	4.6
Increased AST	66	6	58	1.8
Hyperglycemia	65	5	62	2.8
Increased alkaline phosphatase	41	1	37	0.8
Hyponatremia	38	9	28	6
Hypoalbuminemia	36	1.2	30	1.5
Hypocalcemia	32	3.2	29	4.4
Hypokalemia	32	6	24	2.8
Hypophosphatemia	23	6	18	4.5
Hypercalcemia	21	3	24	3.4

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA in combination with chemotherapy followed by KEYTRUDA as a single agent (range: 759 to 777 patients) and placebo in combination with chemotherapy followed by placebo (range: 378 to 389 patients).

† Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

‡ Graded per NCI CTCAE v4.0

Locally Recurrent Unresectable or Metastatic TNBC

The safety of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a multicenter, double-blind, randomized (2:1), placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting *[see Clinical Studies (14.19)]*. A total of 596 patients (including 34 patients from a safety run-in) received KEYTRUDA 200 mg every 3 weeks in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin.

The median duration of exposure to KEYTRUDA was 5.7 months (range: 1 day to 33.0 months).

Fatal adverse reactions occurred in 2.5% of patients receiving KEYTRUDA in combination with chemotherapy, including cardio-respiratory arrest (0.7%) and septic shock (0.3%).

Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin. Serious adverse reactions in ≥2% of patients were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%).

KEYTRUDA was discontinued for adverse reactions in 11% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 50% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (22%), thrombocytopenia (14%), anemia (7%), increased ALT (6%), leukopenia (5%), increased AST (5%), decreased white blood cell count (3.9%), and diarrhea (2%).

Tables 55 and 56 summarize the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

Table 55: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with chemotherapy n=596		Placebo every 3 weeks with chemotherapy n=281	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General				
Fatigue†	48	5	49	4.3
Gastrointestinal				
Nausea	44	1.7	47	1.8
Diarrhea	28	1.8	23	1.8
Constipation	28	0.5	27	0.4
Vomiting	26	2.7	22	3.2
Skin and Subcutaneous Tissue				
Alopecia	34	0.8	35	1.1
Rash‡	26	2	16	0
Respiratory, Thoracic and Mediastinal				
Cough§	23	0	20	0.4
Metabolism and Nutrition				
Decreased appetite	21	0.8	14	0.4
Nervous System				
Headache¶	20	0.7	23	0.7

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash maculo-papular, rash pruritic, rash pustular, rash macular, rash papular, butterfly rash, rash erythematous, eyelid rash
§ Includes cough, productive cough, upper-airway cough syndrome
¶ Includes headache, migraine, tension headache

Table 56: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy		Placebo every 3 weeks with chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	90	20	85	19
Leukopenia	85	39	86	39
Neutropenia	76	49	77	52
Lymphopenia	70	26	70	19
Thrombocytopenia	54	19	53	21
Chemistry				
Increased ALT	60	11	58	8
Increased AST	57	9	55	6
Hyperglycemia	52	4.4	51	2.2
Hypoalbuminemia	37	2.2	32	2.2
Increased alkaline phosphatase	35	3.9	39	2.2
Hypocalcemia	29	3.3	27	1.8
Hyponatremia	28	5	26	6
Hypophosphatemia	21	7	18	4.8
Hypokalemia	20	4.4	18	4.0

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + chemotherapy (range: 566 to 592 patients) and placebo + chemotherapy (range: 269 to 280 patients).
† Graded per NCI CTCAE v4.03

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KEYTRUDA. 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.

Hepatobiliary: sclerosing cholangitis

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *(see Data)*. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects of the PD-1 pathway on reproduction demonstrated that a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.2 Lactation

Risk Summary

There are no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to KEYTRUDA are unknown. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with melanoma, cHL, PMBCL, MCC, MSI-H or dMMR cancer, and TMB-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1, 14.4, 14.5, 14.7, 14.14, 14.17)]*.

In KEYNOTE-051, 173 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive solid tumors received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 25 months). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults included pyrexia (33%), vomiting (29%), headache (25%), abdominal pain (23%), decreased lymphocyte count (13%), and decreased white blood cell count (11%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (31%), neutropenia (28%), thrombocytopenia (22%), and Grade 3 anemia (17%).

The safety and effectiveness of KEYTRUDA in pediatric patients have not been established in the other approved indications *[see Indications and Usage (1)]*.

8.5 Geriatric Use

Of 3781 patients with melanoma, NSCLC, HNSCC, or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 48% were 65 years and over and 17% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of 389 adult patients with cHL who were treated with KEYTRUDA in clinical studies, 46 (12%) were 65 years and over. Patients aged 65 years and over had a higher incidence of serious adverse reactions (50%) than patients aged younger than 65 years (24%). Clinical studies of KEYTRUDA in cHL did not include sufficient numbers of patients aged 65 years and over to determine whether effectiveness differs from that in younger patients.

Of 506 adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC following complete resection and platinum-based chemotherapy who were treated with KEYTRUDA in KEYNOTE-091, 242 (48%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of 596 adult patients with TNBC who were treated with KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin in KEYNOTE-355, 137 (23%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of 406 adult patients with endometrial carcinoma who were treated with KEYTRUDA in combination with lenvatinib in KEYNOTE-775, 201 (50%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of the 564 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in combination with enfortumab vedotin, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with KEYTRUDA in combination with enfortumab vedotin experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Of the 432 patients randomized to KEYTRUDA in combination with axitinib in the KEYNOTE-426 trial, 40% were 65 years or older. No overall difference in safety or efficacy was reported between patients who were ≥65 years of age and younger.

Of 292 adult patients with FIGO 2014 Stage III-IVA cervical cancer who were treated with KEYTRUDA in combination with CRT in KEYNOTE-A18, 42 (14%) were 65 years and over. No overall differences in safety or efficacy were observed between elderly and younger patients.

11 DESCRIPTION

Pembrolizumab is a programmed death receptor-1 (PD 1)-blocking antibody. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

KEYTRUDA (pembrolizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab in 4 mL of

solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

In syngeneic mouse tumor models, combination treatment of a PD-1 blocking antibody and kinase inhibitor lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and reduced tumor growth compared to either treatment alone.

12.2 Pharmacodynamics

There are no clinically significant exposure-response relationships for efficacy or safety at pembrolizumab dosages of 200 mg or 2 mg/kg every 3 weeks regardless of cancer type. There are no clinically significant exposure-response relationships for efficacy or safety at pembrolizumab dosages of 200 mg or 2 mg/kg every 3 weeks and 400 mg every 6 weeks in patients with solid tumors based on observed data in adult patients with melanoma. The exposure-response relationships for efficacy or safety at pembrolizumab dosages of 400 mg every 6 weeks in patients with classical Hodgkin lymphoma or mediastinal large B-cell lymphoma have not been fully characterized.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks.

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Distribution

The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%).

Elimination

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] at steady state than that after the first dose [252 mL/day (37%)]; this decrease in clearance with time is not considered clinically important. The terminal half-life ($t_{1/2}$) is 22 days (32%).

Specific Populations

The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (89% White), renal impairment (eGFR ≥15 mL/min/1.73 m^2), mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST), or tumor burden. The impact of severe hepatic impairment (total bilirubin >3 times ULN and any AST) on the pharmacokinetics of pembrolizumab is unknown.

Pediatric Patients: Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (10 months to 17 years) are comparable to those of adults at the same dose.

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 in this section with the incidence of ADA in other studies, including those of KEYTRUDA or of other pembrolizumab products.

Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the KEYTRUDA-treated patients with a pembrolizumab concentration below the drug tolerance level of the ADA assay.

In clinical studies in patients treated with KEYTRUDA at a dosage of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks, 27 (2.1%) of 1,289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom 6 (0.5%) patients had neutralizing antibodies against pembrolizumab. There were no identified clinically significant effects of ADA on pembrolizumab pharmacokinetics or on the risk of infusion reactions. Because of the low occurrence of ADA, the effect of these ADA on the effectiveness of KEYTRUDA is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1/PD-L1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice and mice receiving PD-L1-blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus. Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-006 (NCT01866319), a randomized (1:1:1), open-label, multicenter, active-controlled trial in 834 patients. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg intravenously every 2 weeks or 10 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review [BICR] using Response Evaluation Criteria in Solid

Tumors [RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ]). Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DoR).

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 66% had no prior systemic therapy for metastatic disease; 69% ECOG PS of 0; 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay; 65% had M1c stage disease; 68% with normal LDH; 36% with reported BRAF mutation-positive melanoma; and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

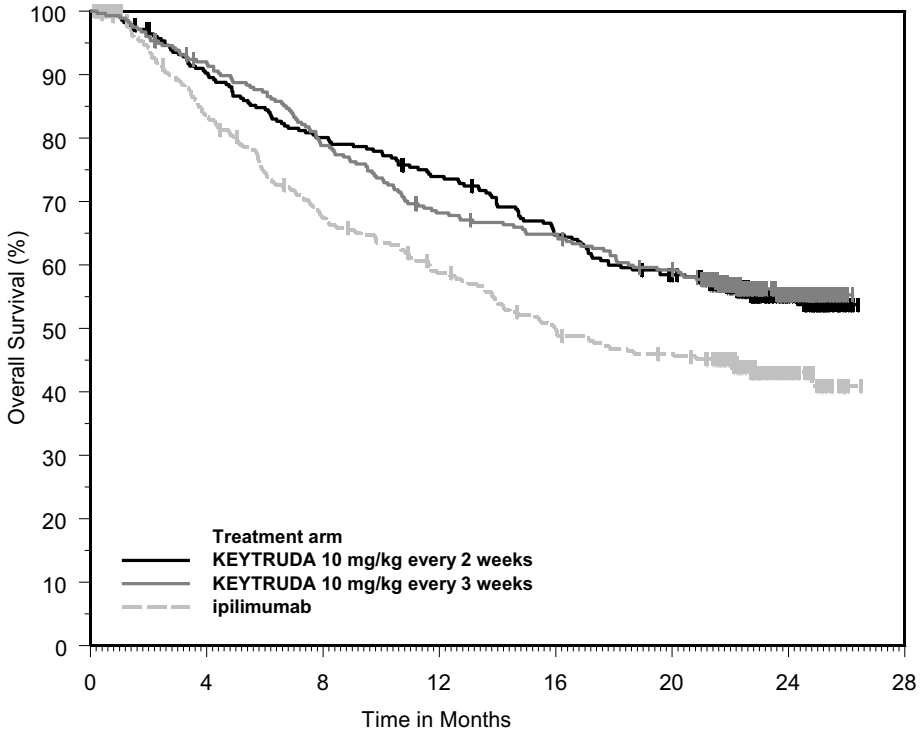
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months. Efficacy results are summarized in Table 57 and Figure 1.

Table 57: Efficacy Results in KEYNOTE-006

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab 3 mg/kg every 3 weeks n=278
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best objective response by BICR			
ORR (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response rate	6%	5%	1%
Partial response rate	27%	29%	10%

* Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

Figure 1: Kaplan-Meier Curve for Overall Survival in KEYNOTE-006*



Number at Risk								
KEYTRUDA 10 mg/kg every 2 weeks:	279	249	221	202	176	156	44	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	251	215	184	174	156	43	0
ipilimumab:	278	213	170	145	122	110	28	0

**Based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)*

Ipilimumab-Refractory Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-002 (NCT01704287), a multicenter, randomized (1:1:1), active-controlled trial in 540 patients randomized to receive one of two doses of KEYTRUDA in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of KEYTRUDA 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 mg/mL/min intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 mg/mL/min plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 mg/mL/min intravenously every 3 weeks (8%). Randomization was stratified by ECOG PS (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. Additional efficacy outcome measures were confirmed ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age of 62 years (range: 15 to 89), 43% age 65 or older; 61% male; 98% White; and 55% ECOG PS of 0 and 45% ECOG PS of 1. Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm. There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive KEYTRUDA. Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months. Efficacy results are summarized in Table 58 and Figure 2.

Table 58: Efficacy Results in KEYNOTE-002

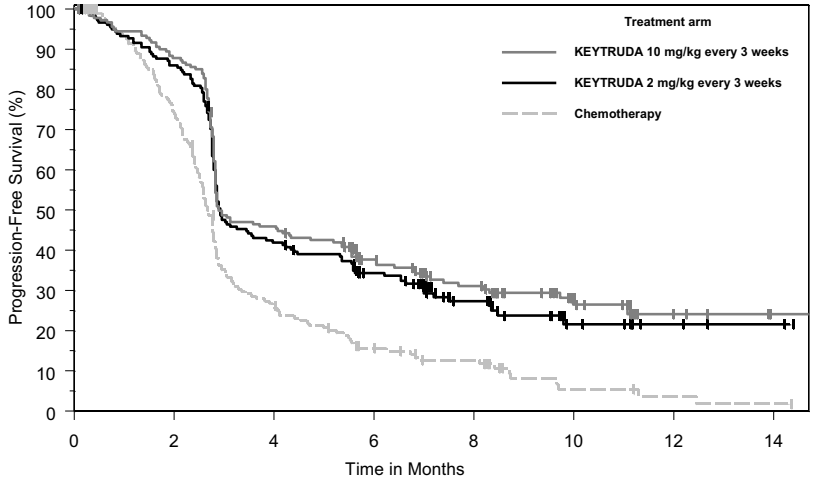
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
p-Value (stratified log-rank)	<0.001	<0.001	---
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
OS†			
Deaths (%)	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value (stratified log-rank)	0.117	0.011‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Objective Response Rate			
ORR (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response rate	2%	3%	0%
Partial response rate	19%	23%	4%

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

† With additional follow-up of 18 months after the PFS analysis

‡ Not statistically significant compared to multiplicity adjusted significance level of 0.01

Figure 2: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-002



Number at Risk

KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

Adjuvant Treatment of Resected Stage IIB or IIC Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-716 (NCT03553836), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected Stage IIB or IIC melanoma. Patients were randomized to KEYTRUDA 200 mg or the pediatric (≥12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by AJCC 8th edition T Stage (>2.0-4.0 mm with ulceration vs. >4.0 mm without ulceration vs. >4.0 mm with ulceration). Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) (defined as the time between the date of randomization and the date of first recurrence [local, in-transit or regional lymph nodes or distant recurrence] or death, whichever occurred first). New primary melanomas were excluded from the definition of RFS. Distant metastasis-free survival (DMFS), defined as a spread of tumor to distant organs or distant lymph nodes, was an additional efficacy outcome measure. Patients underwent imaging every six months for one year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

The study population characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; 98% White; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had Stage IIB and 35% had Stage IIC.

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 59 and Figure 3.

Table 59: Efficacy Results in KEYNOTE-716

Endpoint	KEYTRUDA 200 mg every 3 weeks n=487	Placebo n=489
RFS		
Number (%) of patients with event	54 (11%)	82 (17%)
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio*,† (95% CI)	0.65 (0.46, 0.92)	
p-Value†	0.0132‡	
DMFS		
Number (%) of patients with event	63 (13%)	95 (19%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio*,† (95% CI)	0.64 (0.47, 0.88)	
p-Value†	0.0058§	

* Based on the stratified Cox proportional hazard model

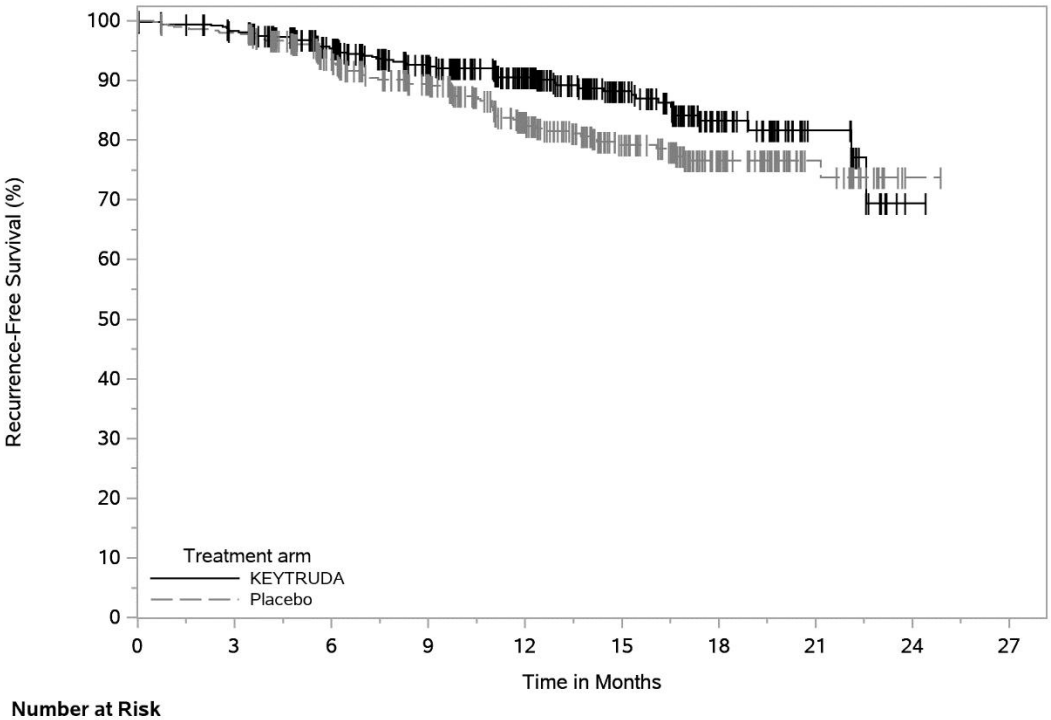
† Based on a log-rank test stratified by American Joint Committee on Cancer 8th edition (AJCC) stage

‡ p-Value is compared with 0.0202 of the allocated alpha for this interim analysis.

§ p-Value is compared with 0.0256 of the allocated alpha for this interim analysis.

NR = not reached

Figure 3: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716



Number at Risk

KEYTRUDA	487	465	401	340	249	149	71	21	1	0
Placebo	489	475	400	336	229	149	77	27	1	0

Adjuvant Treatment of Stage III Resected Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-054 (NCT02362594), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected Stage IIIA (>1 mm lymph node metastasis), IIIB, or IIIC melanoma. Patients were randomized to KEYTRUDA 200 mg intravenously every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. New primary melanomas were excluded from the definition of RFS. DMFS in the whole population and in the population with PD-L1 positive tumors were additional efficacy outcome measures. DMFS was defined as a spread of tumor to distant organs or distant lymph nodes. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had Stage IIIA, 46% had Stage IIIB, 18% had Stage IIIC (1-3 positive lymph nodes), and 20% had Stage IIIC (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IUO assay.

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 60 and Figure 4.

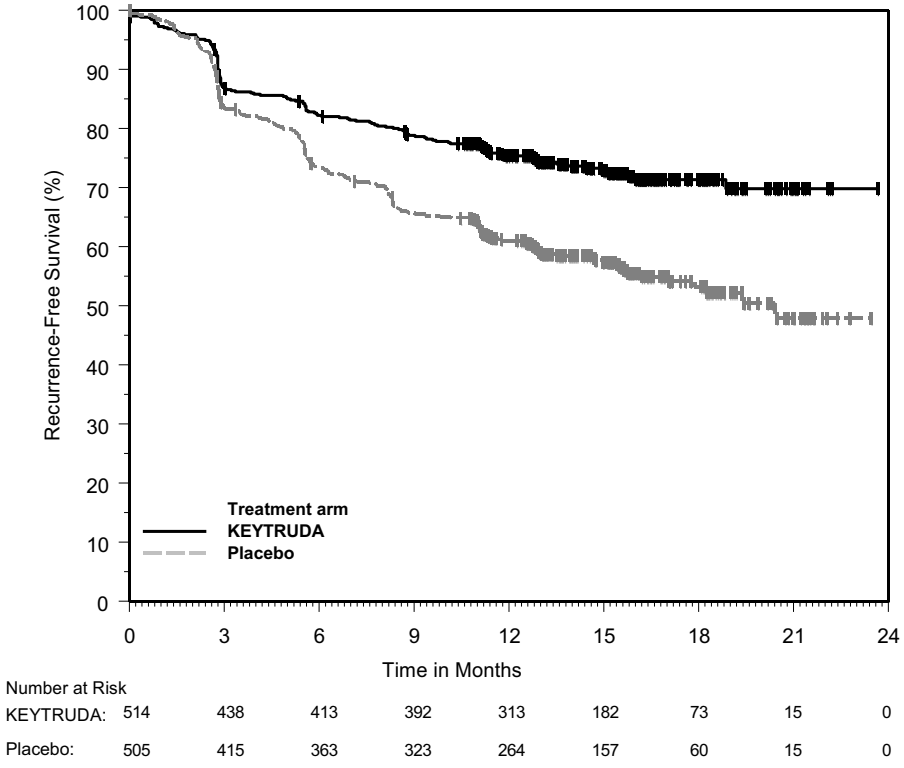
Table 60: Efficacy Results in KEYNOTE-054

Endpoint	KEYTRUDA 200 mg every 3 weeks n=514	Placebo n=505
RFS		
Number (%) of patients with event	135 (26%)	216 (43%)
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio*,† (95% CI)	0.57 (0.46, 0.70)	
p-Value† (log-rank)	<0.001±	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
Median in months (95% CI)	NR (49.6, NR)	40.0 (27.7, NR)
Hazard ratio*,† (95% CI)	0.60 (0.49, 0.73)	
p-Value† (log-rank)	<0.0001§	

* Based on the stratified Cox proportional hazard model
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage
± p-Value is compared with 0.016 of the allocated alpha for this interim analysis.
§ p-Value is compared with 0.028 of the allocated alpha for this analysis.
NR = not reached

For patients with PD-L1 positive tumors, the RFS HR was 0.54 (95% CI: 0.42, 0.69); p<0.0001. For patients with PD-L1 positive tumors, the DMFS HR was 0.61 (95% CI: 0.49, 0.76); p<0.0001. The RFS and DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054



14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1

tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms:

- KEYTRUDA 200 mg, pemetrexed 500 mg/m^2, and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo, pemetrexed 500 mg/m^2, and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 intravenously every 3 weeks.

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Patients randomized to placebo and chemotherapy were offered KEYTRUDA as a single agent at the time of disease progression. Assessment of tumor status was performed at Week 6, Week 12, and then every 9 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG PS of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% [negative]. Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/PD-L1 monoclonal antibody at the time of disease progression.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 61 and Figure 5 summarize the efficacy results for KEYNOTE-189.

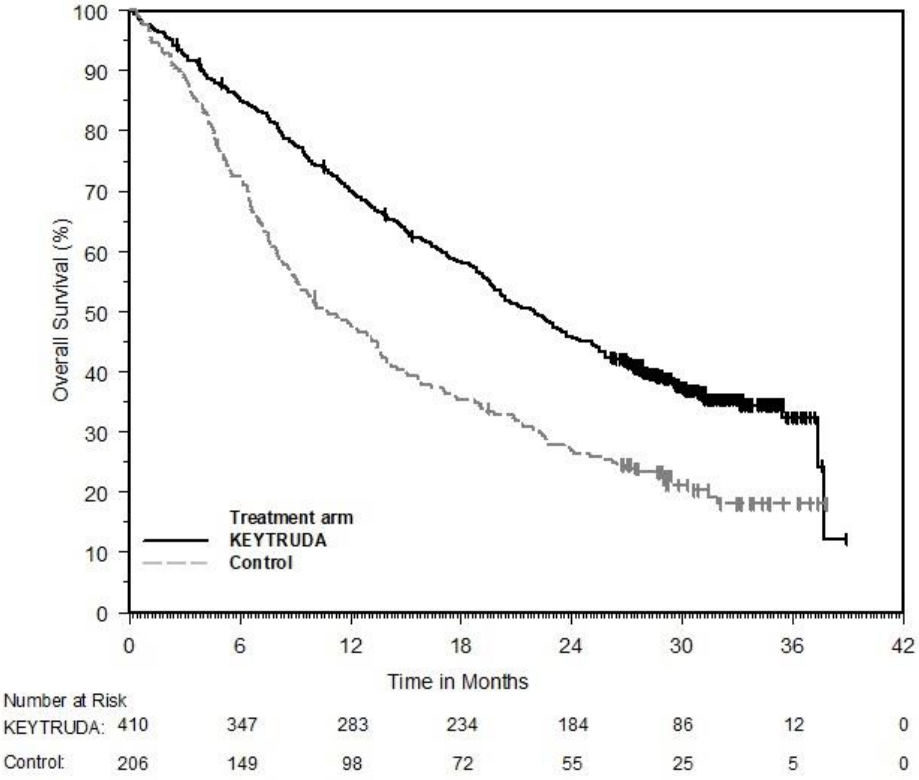
Table 61: Efficacy Results in KEYNOTE-189

Endpoint	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=410	Placebo Pemetrexed Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Median in months (95% CI)	NR (NR, NR)	11.3 (8.7, 15.1)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.0001	
PFS		
Number of patients with event (%)	245 (60%)	166 (81%)
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy, and smoking status
NR = not reached

At the protocol-specified final OS analysis, the median in the KEYTRUDA in combination with pemetrexed and platinum chemotherapy arm was 22.0 months (95% CI: 19.5, 24.5) compared to 10.6 months (95% CI: 8.7, 13.6) in the placebo with pemetrexed and platinum chemotherapy arm, with an HR of 0.56 (95% CI: 0.46, 0.69).

Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-189*



*Based on the protocol-specified final OS analysis

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy

The efficacy of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%), choice of paclitaxel or paclitaxel protein-bound, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with KEYTRUDA and chemotherapy or placebo and chemotherapy continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients randomized to the placebo and chemotherapy arm were offered KEYTRUDA as a single agent at the time

of disease progression. Assessment of tumor status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The main efficacy outcome measures were PFS and ORR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. An additional efficacy outcome measure was DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 29 to 88), 55% age 65 or older; 81% male; 77% White; 71% ECOG PS of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS <1%; 19% were from the East Asian region; and 60% received paclitaxel.

The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 62 and Figure 6 summarize the efficacy results for KEYNOTE-407.

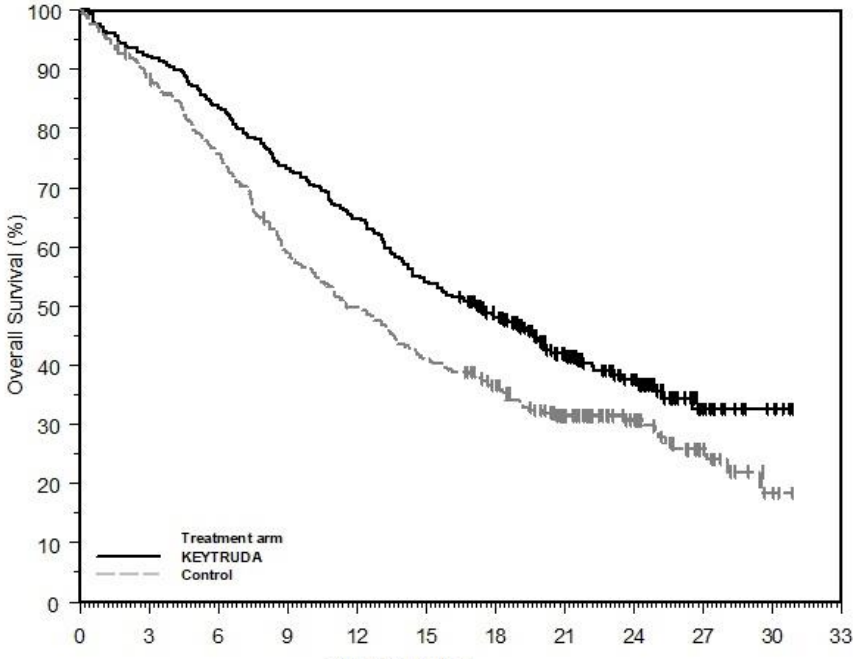
Table 62: Efficacy Results in KEYNOTE-407

Endpoint	**KEYTRUDA 200 mg every 3 weeks Carboplatin Paclitaxel/Paclitaxel protein-bound n=278**	**Placebo Carboplatin Paclitaxel/Paclitaxel protein-bound n=281**
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NE)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value†	0.0017	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.2, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value†	<0.0001	
	n=101	**n=103**
Objective Response Rate‡		
ORR (95% CI)	58% (48, 68)	35% (26, 45)
Difference (95% CI)	23.6% (9.9, 36.4)	
p-Value§	0.0008	
Duration of Response‡		
Median duration of response in months (range)	7.2 (2.4, 12.4+)	4.9 (2.0, 12.4+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ ORR primary analysis and DoR analysis were conducted with the first 204 patients enrolled.
§ Based on a stratified Miettinen-Nurminen test
NE = not estimable

At the protocol-specified final OS analysis, the median in the KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm was 17.1 months (95% CI: 14.4, 19.9) compared to 11.6 months (95% CI: 10.1, 13.7) in the placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm, with an HR of 0.71 (95% CI: 0.58, 0.88).

Figure 6: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407*



Number at Risk												
KEYTRUDA:	278	256	232	203	180	150	119	80	46	14	4	0
Control:	281	245	210	163	137	113	91	61	36	16	3	0

*Based on the protocol-specified final OS analysis

First-line treatment of metastatic NSCLC as a single agent

KEYNOTE-042

The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with Stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥50% vs. TPS 1 to 49%). Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of either of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies.

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Treatment with KEYTRUDA could be reinitiated at the time of subsequent disease

progression and administered for up to 12 months. Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measure was OS in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC. Additional efficacy outcome measures were PFS and ORR in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Sixty-nine percent had ECOG PS of 1; 39% with squamous and 61% with nonsquamous histology; 87% had M1 disease and 13% had Stage IIIA (2%) or Stage IIIB (11%) and who were not candidates for surgical resection or definitive chemoradiation per investigator assessment; and 5% with treated brain metastases at baseline. Forty-seven percent of patients had TPS ≥50% NSCLC and 53% had TPS 1 to 49% NSCLC.

The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 63 and Figure 7 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

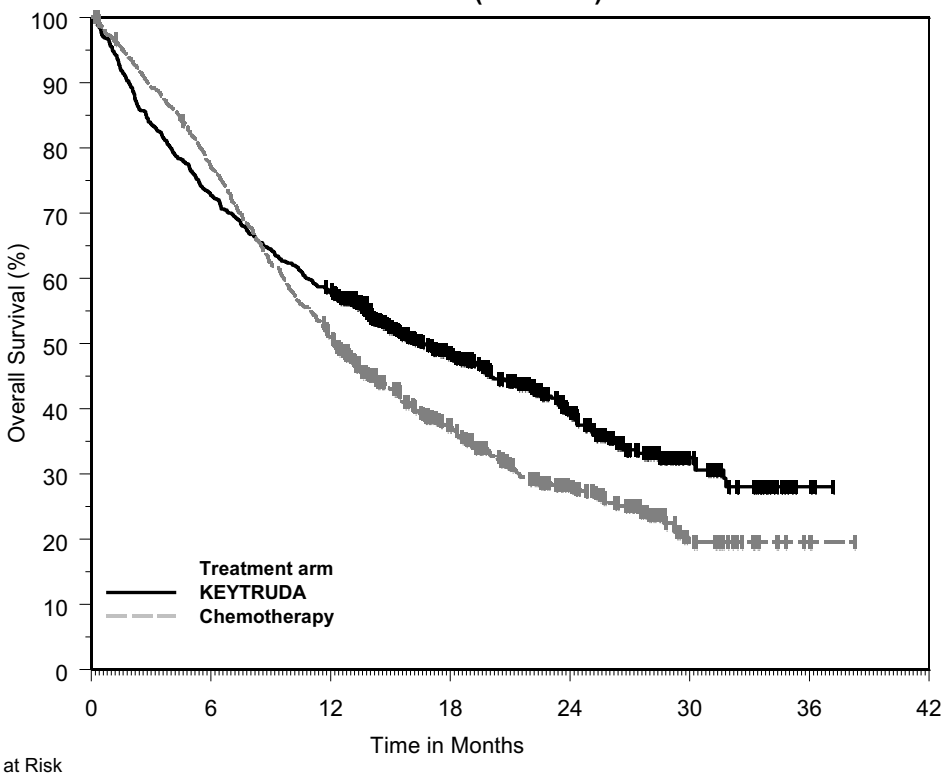
Table 63: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	TPS ≥1%		**TPS ≥50%**	
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=637**	**Chemotherapy n=637**	**KEYTRUDA 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS				
Number of events (%)	371 (58%)	438 (69%)	157 (53%)	199 (66%)
Median in months (95% CI)	16.7 (13.9, 19.7)	12.1 (11.3, 13.3)	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)
Hazard ratio* (95% CI)	0.81 (0.71, 0.93)		0.69 (0.56, 0.85)	
p-Value†	0.0036		0.0006	
PFS				
Number of events (%)	507 (80%)	506 (79%)	221 (74%)	233 (78%)
Median in months (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)	6.9 (5.9, 9.0)	6.4 (6.1, 6.9)
Hazard ratio*,‡ (95% CI)	1.07 (0.94, 1.21)		0.82 (0.68, 0.99)	
p-Value†	-‡		NS§	
Objective Response Rate				
ORR‡ (95% CI)	27% (24, 31)	27% (23, 30)	39% (33.9, 45.3)	32% (26.8, 37.6)
Complete response rate	0.5%	0.5%	0.7%	0.3%
Partial response rate	27%	26%	39%	32%
Duration of Response				
% with duration ≥12 months¶	47%	16%	42%	17%
% with duration ≥18 months¶	26%	6%	25%	5%

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test; compared to a p-Value boundary of 0.0291
‡ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints
§ Not significant compared to a p-Value boundary of 0.0291
¶ Based on observed duration of response

The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≥50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11).

Figure 7: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-042 (TPS ≥1%)



Number at Risk

KEYTRUDA:	637	463	365	214	112	35	2	0
Chemotherapy:	637	485	316	166	88	24	1	0

KEYNOTE-024

The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were eligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of any of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for nonsquamous histologies).

Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression.

The main efficacy outcome measure was PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were OS and ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 33 to 90), 54% age 65 or older; 61% male; 82% White and 15% Asian; 65% with ECOG PS of 1; 18% with squamous and 82% with nonsquamous histology and 9% with history of brain metastases. A total of 66 patients in the chemotherapy arm received KEYTRUDA at the time of disease progression.

The trial demonstrated a statistically significant improvement in both PFS and OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 64 and Figure 8 summarize the efficacy results for KEYNOTE-024.

Table 64: Efficacy Results in KEYNOTE-024

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Median in months (95% CI)†	30.0 (18.3, NR)	14.2 (9.8, 19.0)
Hazard ratio* (95% CI)	0.60 (0.41, 0.89)	
p-Value (stratified log-rank)	0.005‡	
Objective Response Rate		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

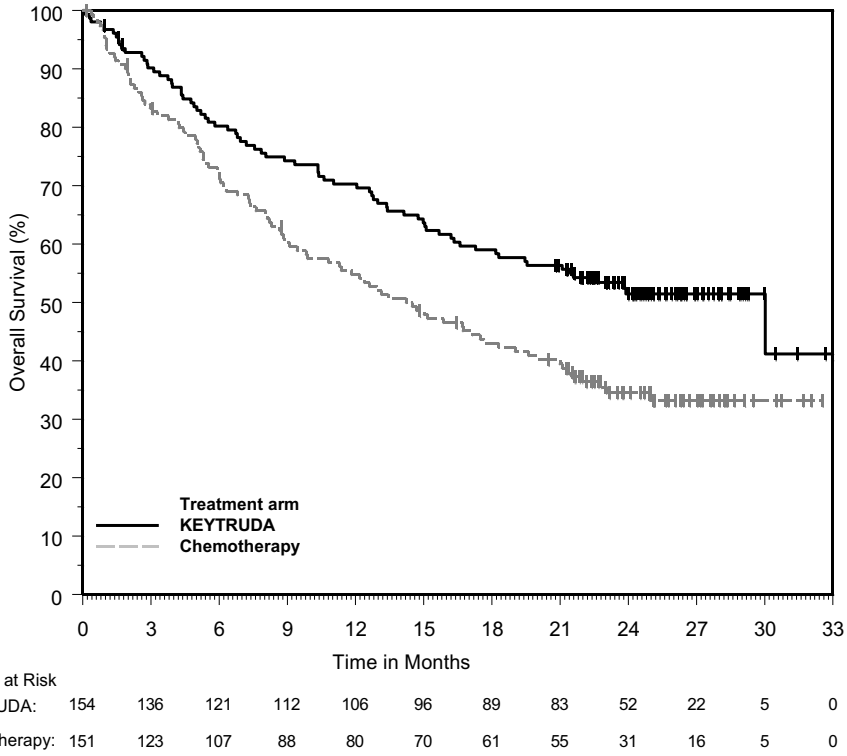
* Based on the stratified Cox proportional hazard model for the interim analysis

† Based on the protocol-specified final OS analysis conducted at 169 events, which occurred 14 months after the interim analysis.

‡ p-Value is compared with 0.0118 of the allocated alpha for the interim analysis

NR = not reached

Figure 8: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024*



*Based on the protocol-specified final OS analysis conducted at 169 events, which occurred 14 months after the interim analysis.

Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG PS (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA 2 mg/kg intravenously every 3 weeks, KEYTRUDA 10 mg/kg intravenously every 3 weeks or docetaxel intravenously 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression. Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and DoR in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 65 and 66 and Figure 9 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 65: Efficacy Results of the Subgroup of Patients with TPS ≥50% in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=139	KEYTRUDA 10 mg/kg every 3 weeks n=151	Docetaxel 75 mg/m^2 every 3 weeks n=152
OS			
Deaths (%)	58 (42%)	60 (40%)	86 (57%)
Median in months (95% CI)	14.9 (10.4, NR)	17.3 (11.8, NR)	8.2 (6.4, 10.7)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	89 (64%)	97 (64%)	118 (78%)
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Objective Response Rate			
ORR† (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 16.8+)	NR (2.1+, 17.8+)	8.1 (2.1+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Table 66: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

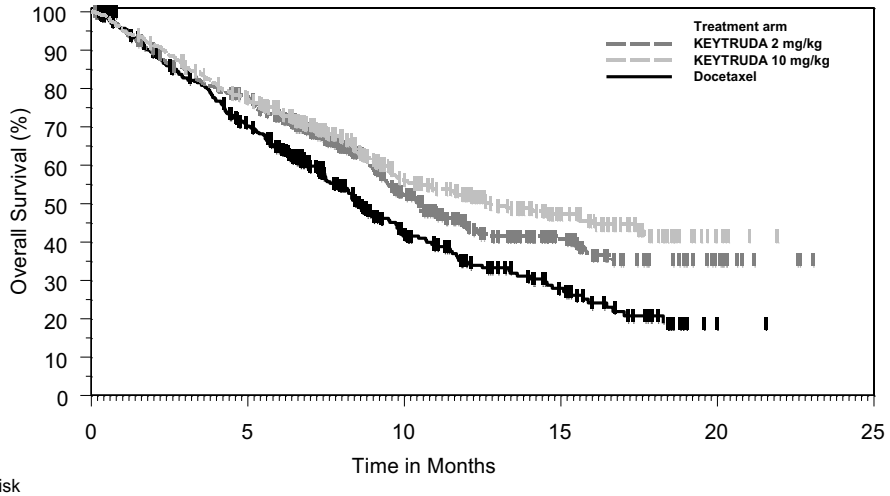
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	266 (77%)	255 (74%)	257 (75%)
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value (stratified log-rank)	0.068	0.005	---
Objective Response Rate			
ORR† (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Figure 9: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-010 (TPS ≥1%)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	259	115	49	12	0
KEYTRUDA 10 mg/kg:	346	255	124	56	6	0
Docetaxel:	343	212	79	33	1	0

Neoadjuvant and adjuvant treatment of resectable NSCLC

The efficacy of KEYTRUDA in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-671 (NCT03425643), a multicenter, randomized, double-blind, placebo-controlled trial conducted in 797 patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition. Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or a history of interstitial lung disease or pneumonitis that required steroids were ineligible. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS ≥50% or <50%), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia).

Patients were randomized (1:1) to one of the following treatment arms:

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, KEYTRUDA 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Additional efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review.

The study population characteristics were: median age of 64 years (range: 26 to 83); 45% age 65 or older and 7% age 75 or older; 71% male; 61% White, 31% Asian, 2% Black, 4% race not reported; 9% Hispanic or Latino; 63% ECOG PS of 0 and 37% ECOG PS of 1. Thirty percent had Stage II and 70% had Stage III disease; 33% had TPS ≥50% and 67% had TPS <50%; 43% had tumors with squamous histology and 57% had tumors with non-squamous histology; 31% were from the East Asian region.

Eighty-one percent of patients in the KEYTRUDA in combination with platinum-containing chemotherapy arm received definitive surgery compared to 76% of patients in the placebo in combination with platinum-containing chemotherapy arm.

The trial demonstrated statistically significant improvements in OS and EFS for patients randomized to KEYTRUDA in combination with platinum-containing chemotherapy followed by KEYTRUDA as a single agent compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone.

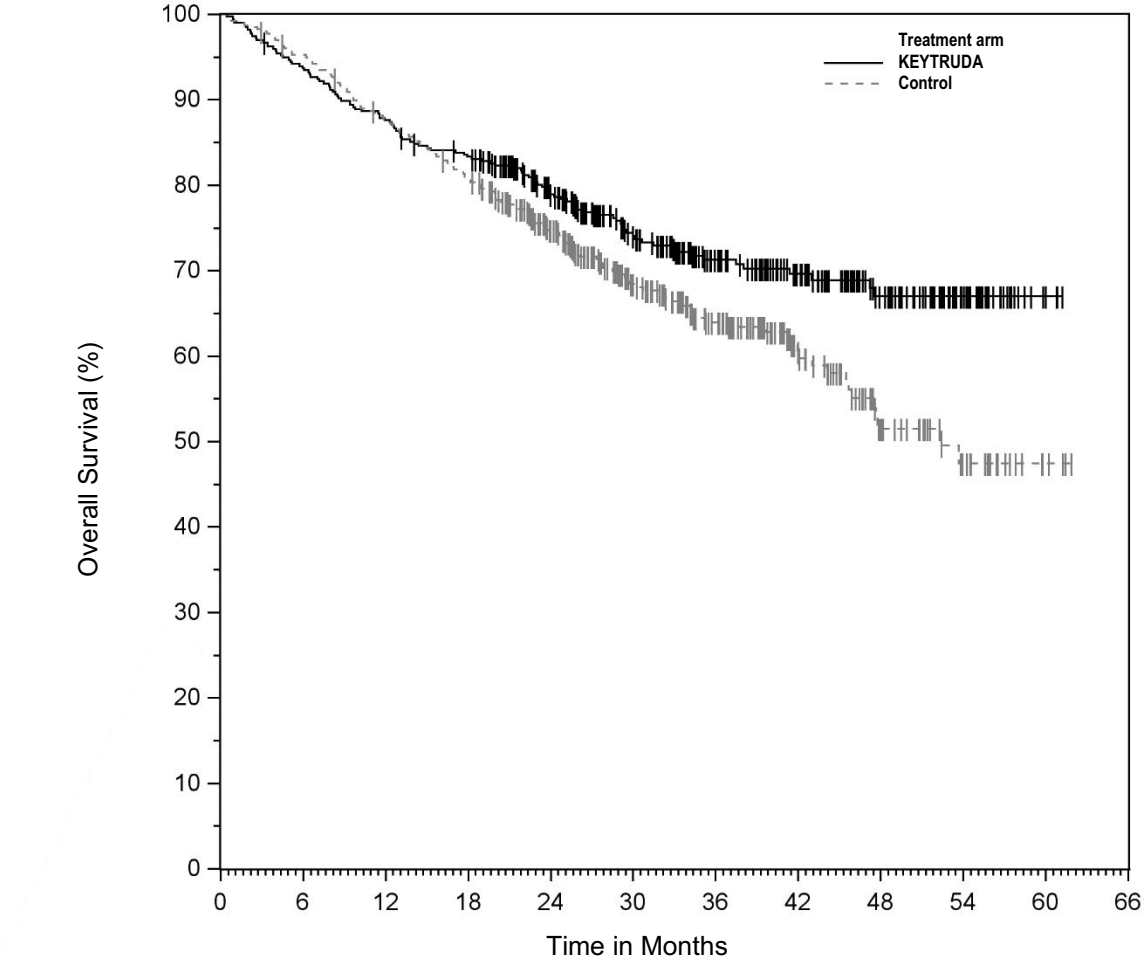
Table 67 and Figure 10 summarize the efficacy results for KEYNOTE-671.

Table 67: Efficacy Results in KEYNOTE-671

Endpoint	KEYTRUDA 200 mg every 3 weeks with chemotherapy/KEYTRUDA n=397	Placebo with chemotherapy/Placebo n=400
OS		
Number of patients with event (%)	110 (28%)	144 (36%)
Median in months* (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.93)	
p-Value‡,§	0.0103	
EFS		
Number of patients with event (%)	139 (35%)	205 (51%)
Median in months* (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)
Hazard ratio† (95% CI)	0.58 (0.46, 0.72)	
p-Value‡,¶	<0.0001	

* Based on Kaplan-Meier estimates
† Based on Cox regression model with treatment as a covariate stratified by stage, tumor PD-L1 expression, histology, and geographic region
‡ Based on stratified log-rank test
§ Compared to a two-sided p-Value boundary of 0.0109
¶ Compared to a two-sided p-Value boundary of 0.0092
NR = not reached

Figure 10: Kaplan-Meier Curve for Overall Survival in KEYNOTE-671



The trial demonstrated a statistically significant difference in pCR rate (18.1% vs. 4.0%; p<0.0001) and mPR rate (30.2% vs. 11.0%; p<0.0001).

Adjuvant treatment of resected NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-091 (NCT02504372), a multicenter, randomized, triple-blind, placebo-controlled trial conducted in 1177 patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC by AJCC 7th edition. Patients had not received neoadjuvant radiotherapy or chemotherapy. Adjuvant chemotherapy up to 4 cycles was optional. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis. Randomization was stratified by stage (IB vs. II vs. IIIA), receipt of adjuvant chemotherapy (yes vs. no), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS ≥50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST v1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity or up to one year. Tumor assessments were conducted every 12 weeks for the first year, then every 6 months for years 2 to 3, and then annually through year 5. After year 5, imaging was

performed as per local standard of care. The major efficacy outcome measure was investigator-assessed disease-free survival (DFS). An additional efficacy outcome measure was OS.

Of 1177 patients randomized, 1010 (86%) received adjuvant platinum-based chemotherapy following resection. Among these 1010 patients, the median age was 64 years (range: 35 to 84), 49% age 65 or older; 68% male; 77% White, 18% Asian; 86% current or former smokers; and 39% with ECOG PS of 1. Eleven percent had Stage IB, 57% had Stage II, and 31% had Stage IIIA disease. Thirty-nine percent had PD-L1 TPS <1% [negative], 33% had TPS 1-49%, and 28% had TPS ≥50%. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The trial met its primary endpoint, demonstrating a statistically significant improvement in DFS in the overall population for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). OS results were not mature with only 42% of pre-specified OS events in the overall population.

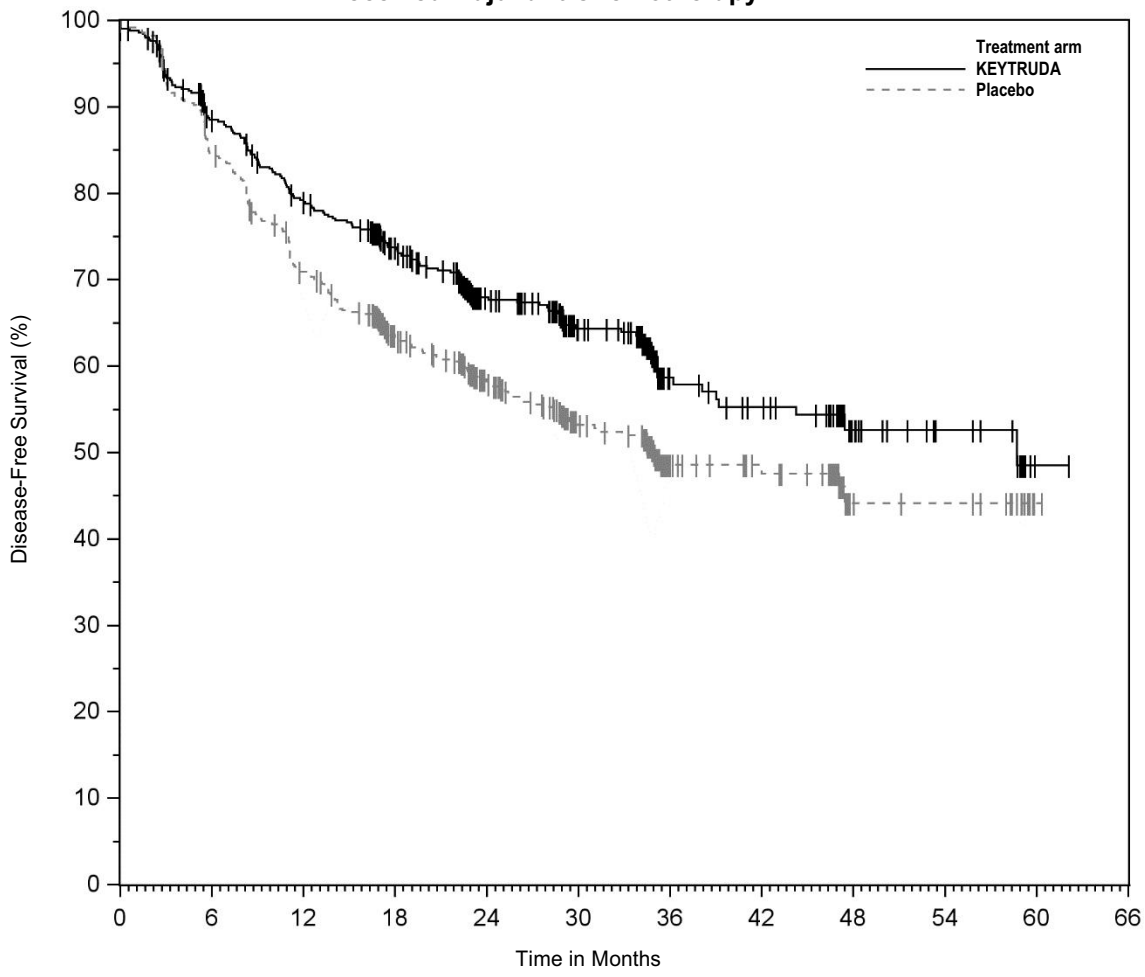
Table 68 and Figure 11 summarize the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

Table 68: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=506**	**Placebo n=504**
DFS		
Number (%) of patients with event	177 (35%)	231 (46%)
Median in months (95% CI)	58.7 (39.2, NR)	34.9 (28.6, NR)
Hazard ratio* (95% CI)	0.73 (0.60, 0.89)	

* Based on the unstratified univariate Cox regression model
NR = not reached

Figure 11: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy



Number at Risk												
KEYTRUDA	506	422	372	308	227	158	71	61	27	16	1	0
Placebo	504	422	349	272	206	134	58	47	17	15	1	0

14.3 Head and Neck Squamous Cell Cancer

First-line treatment of metastatic or unresectable, recurrent HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks
- KEYTRUDA 200 mg intravenously every 3 weeks, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m^2 intravenously every 3 weeks, and FU 1000 mg/m^2/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)

- Cetuximab 400 mg/m^2 intravenously as the initial dose then 250 mg/m^2 intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m^2 intravenously every 3 weeks, and FU 1000 mg/m^2/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months. A retrospective re-classification of patients' tumor PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx kit was conducted using the tumor specimens used for randomization.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) sequentially tested in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1, and the overall population.

The study population characteristics were: median age of 61 years (range: 20 to 94), 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20.

The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. Table 69 and Figure 12 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

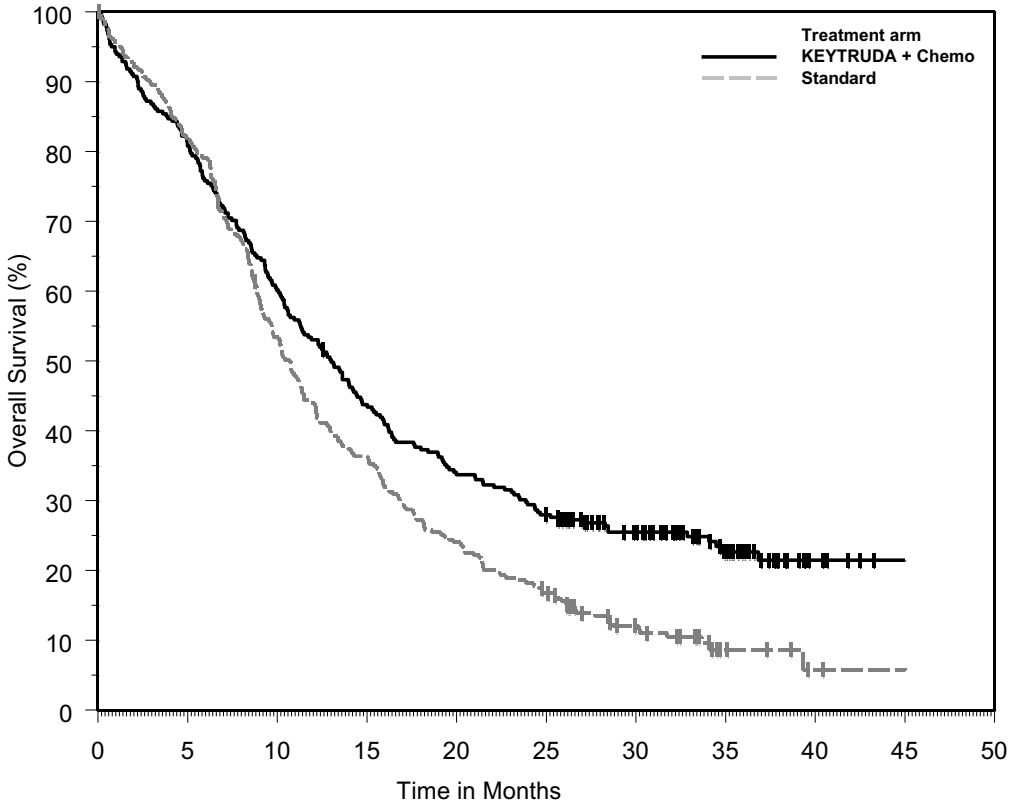
Table 69: Efficacy Results* for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

Endpoint	KEYTRUDA 200 mg every 3 weeks Platinum FU n=281	Cetuximab Platinum FU n=278
OS		
Number (%) of patients with event	197 (70%)	223 (80%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio† (95% CI)	0.77 (0.63, 0.93)	
p-Value‡	0.0067	
PFS		
Number of patients with event (%)	244 (87%)	253 (91%)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
Hazard ratio† (95% CI)	0.92 (0.77, 1.10)	
p-Value‡	0.3394	
Objective Response Rate		
ORR§ (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response rate	6%	3%
Partial response rate	30%	33%
Duration of Response		
Median in months (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)

* Results at a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

At the pre-specified final OS analysis for the ITT population, the hazard ratio was 0.72 (95% CI: 0.60, 0.87). In addition, KEYNOTE-048 demonstrated a statistically significant improvement in OS for the subgroups of patients with PD-L1 CPS ≥1 (HR=0.65, 95% CI: 0.53, 0.80) and CPS ≥20 (HR=0.60, 95% CI: 0.45, 0.82).

Figure 12: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048*



Number at Risk											
KEYTRUDA + Chemo:	281	227	169	122	94	77	55	29	5	0	0
Standard:	278	227	147	100	66	45	23	6	1	0	0

* At the time of the protocol-specified final analysis.

The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis. At the time of the interim and final analyses, there was no significant difference in OS between the KEYTRUDA single agent arm and the control arm for the overall population.

Table 70 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 13 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

Table 70: Efficacy Results* for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

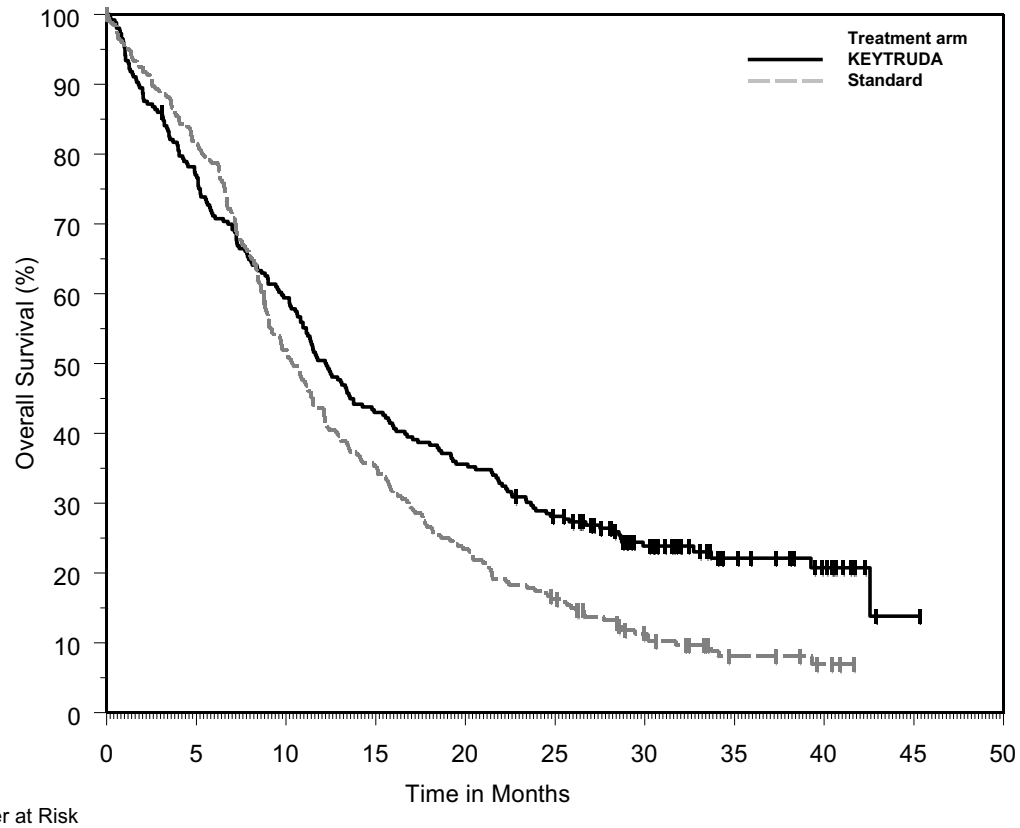
Endpoint	CPS ≥1		CPS ≥20	
	KEYTRUDA 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	KEYTRUDA 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio† (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value‡	0.0171		0.0015	
PFS				
Number of events (%)	225 (88%)	231 (91%)	113 (85%)	111 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
Hazard ratio† (95% CI)	1.15 (0.95, 1.38)		0.97 (0.74, 1.27)	
Objective Response Rate				
ORR§ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)	23% (16.4, 31.4)	36% (27.6, 45.3)
Complete response rate	5%	3%	8%	3%
Partial response rate	14%	32%	16%	33%
Duration of Response				
Median in months (range)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)	20.9 (2.7, 34.8+)	4.2 (1.2+, 22.3+)

* Results at a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ Based on a stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

At the pre-specified final OS analysis comparing KEYTRUDA as a single agent to cetuximab in combination with chemotherapy, the hazard ratio for the subgroup of patients with CPS ≥1 was 0.74 (95% CI: 0.61, 0.90) and the hazard ratio for the subgroup of patients with CPS ≥20 was 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC at the time of the pre-specified final OS analysis, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.86 (95% CI: 0.66, 1.12).

Figure 13: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1)*



Number at Risk											
KEYTRUDA:	257	197	152	110	91	70	43	21	13	1	0
Standard:	255	207	131	89	59	40	21	9	5	0	0

* At the time of the protocol-specified final analysis.

Previously treated recurrent or metastatic HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-012 (NCT01848834), a multicenter, non-randomized, open-label, multi-cohort study that enrolled 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS ≥2 were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

The study population characteristics were median age of 60 years, 32% age 65 or older; 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, the median DoR had not been reached (range: 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and DoR were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

14.4 Classical Hodgkin Lymphoma

KEYNOTE-204

The efficacy of KEYTRUDA was investigated in KEYNOTE-204 (NCT02684292), a randomized, open-label, active controlled trial conducted in 304 patients with relapsed or refractory cHL. The trial enrolled adults with relapsed or refractory disease after at least one multi-agent chemotherapy regimen. Patients were randomized (1:1) to receive:

- KEYTRUDA 200 mg intravenously every 3 weeks or
- Brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks

Treatment was continued until unacceptable toxicity, disease progression, or a maximum of 35 cycles (up to approximately 2 years). Disease assessment was performed every 12 weeks. Randomization was stratified by prior autologous HSCT (yes vs. no) and disease status after frontline therapy (primary refractory vs. relapse <12 months after completion vs. relapse ≥12 months after completion). The main efficacy measure was PFS as assessed by BICR using 2007 revised International Working Group criteria.

The study population characteristics were: median age of 35 years (range: 18 to 84); 57% male; 77% White, 9% Asian, 3.9% Black. The median number of prior therapies was 2 (range: 1 to 10) in the KEYTRUDA arm and 3 (range: 1 to 11) in the BV arm, with 18% in both arms having 1 prior line. Forty-two percent of patients were refractory to the last prior therapy, 29% had primary refractory disease, 37% had prior autologous HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

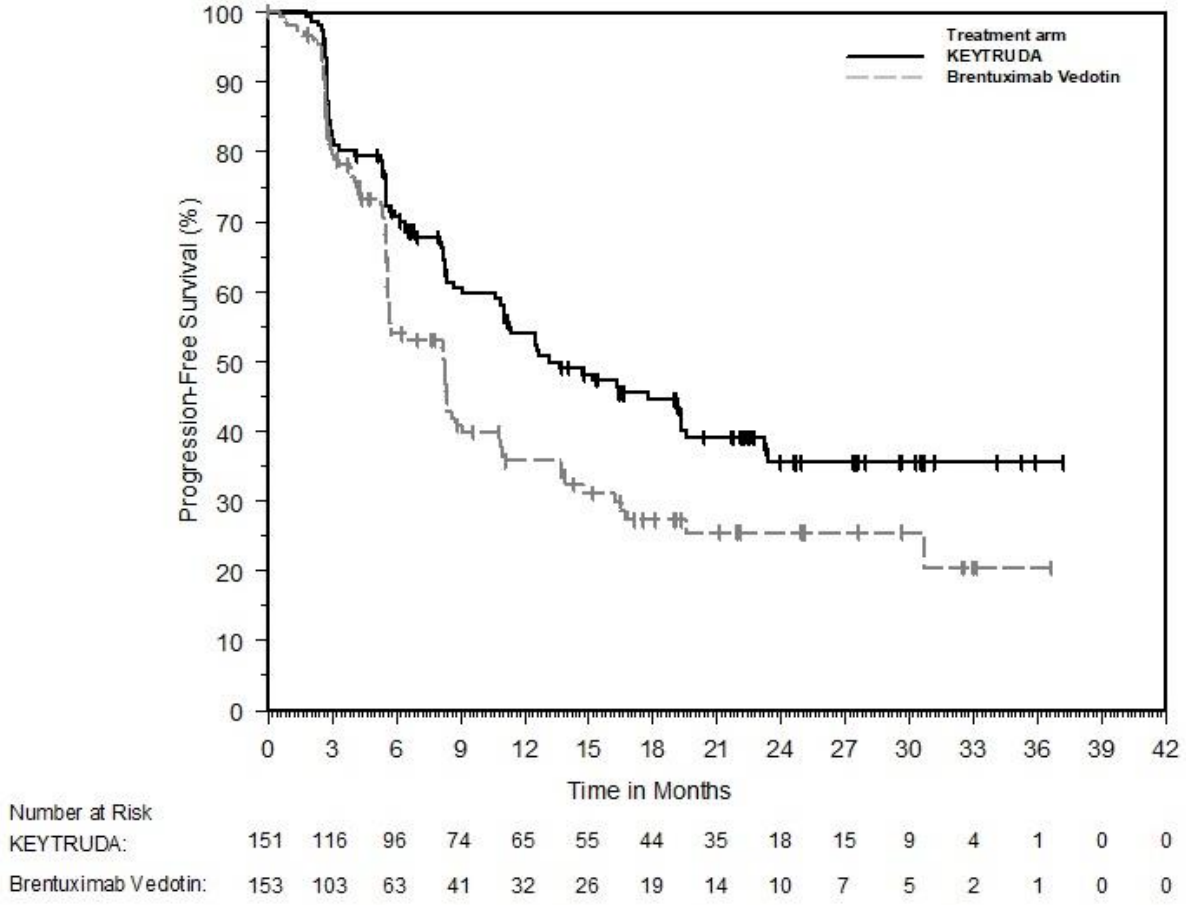
Efficacy is summarized in Table 71 and Figure 14.

Table 71: Efficacy Results in Patients with cHL in KEYNOTE-204

Endpoint	KEYTRUDA 200 mg every 3 weeks n=151	Brentuximab Vedotin 1.8 mg/kg every 3 weeks n=153
PFS		
Number of patients with event (%)	81 (54%)	88 (58%)
Median in months (95% CI)*	13.2 (10.9, 19.4)	8.3 (5.7, 8.8)
Hazard ratio† (95% CI)	0.65 (0.48, 0.88)	
p-Value‡	0.0027	
Objective Response Rate		
ORR§ (95% CI)	66% (57, 73)	54% (46, 62)
Complete response	25%	24%
Partial response	41%	30%
Duration of Response		
Median in months (range)*	20.7 (0.0+, 33.2+)	13.8 (0.0+, 33.9+)

* Based on Kaplan-Meier estimates.
† Based on the stratified Cox proportional hazard model.
‡ Based on a stratified log-rank test. One-sided p-Value, with a prespecified boundary of 0.0043.
§ Difference in ORR is not statistically significant.
\+ Denotes a censored value.

Figure 14: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204



KEYNOTE-087

The efficacy of KEYTRUDA was investigated in KEYNOTE-087 (NCT02453594), a multicenter, non-randomized, open-label trial in 210 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or >5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients who did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, Complete Response Rate, and DoR) were assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

The study population characteristics were: median age of 35 years (range: 18 to 76), 9% age 65 or older; 54% male; 88% White; and 49% ECOG PS of 0 and 51% ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range: 1 to 12). Fifty-eight percent were refractory to the last prior therapy, including 35% with primary refractory disease and 14% whose disease was chemo-refractory to all prior regimens. Sixty-one percent of patients had undergone prior autologous HSCT, 83% had received prior brentuximab vedotin and 36% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-087 are summarized in Table 72.

Table 72: Efficacy Results in Patients with cHL in KEYNOTE-087

Endpoint	KEYTRUDA 200 mg every 3 weeks n=210*
Objective Response Rate	
ORR (95% CI)	69% (62, 75)
Complete response rate	22%
Partial response rate	47%
Duration of Response	
Median in months (range)	11.1 (0.0+, 11.1)†

* Median follow-up time of 9.4 months

† Based on patients (n=145) with a response by independent review

14.5 Primary Mediastinal Large B-Cell Lymphoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-170 (NCT02576990), a multicenter, open-label, single-arm trial in 53 patients with relapsed or refractory PMBCL. Patients were not eligible if they had active non-infectious pneumonitis, allogeneic HSCT within the past 5 years (or >5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy. Patients were treated with KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months for patients who did not progress. Disease assessments were performed every 12 weeks and assessed by BICR according to the 2007 revised IWG criteria. The efficacy outcome measures were ORR and DoR.

The study population characteristics were: median age of 33 years (range: 20 to 61 years); 43% male; 92% White; and 43% ECOG PS of 0 and 57% ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of PMBCL was 3 (range 2 to 8). Thirty-six percent had primary refractory disease, 49% had relapsed disease refractory to the last prior therapy, and 15% had untreated relapse. Twenty-six percent of patients had undergone prior autologous HSCT, and 32% of patients had prior radiation therapy. All patients had received rituximab as part of a prior line of therapy.

For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months). Efficacy results for KEYNOTE-170 are summarized in Table 73.

Table 73: Efficacy Results in Patients with PMBCL in KEYNOTE-170

Endpoint	KEYTRUDA 200 mg every 3 weeks n=53*
Objective Response Rate	
ORR (95% CI)	45% (32, 60)
Complete response rate	11%
Partial response rate	34%
Duration of Response	
Median in months (range)	NR (1.1+, 19.2+)†

* Median follow-up time of 9.7 months

† Based on patients (n=24) with a response by independent review

NR = not reached

14.6 Urothelial Cancer

In Combination with Enfortumab Vedotin for the Treatment of Patients with Urothelial Cancer

The efficacy of KEYTRUDA in combination with enfortumab vedotin was evaluated in KEYNOTE-A39 (NCT04223856), an open-label, randomized, multicenter trial that enrolled 886 patients with locally advanced or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded.

Patients were randomized 1:1 to receive either:

- KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle. KEYTRUDA was given approximately 30 minutes after enfortumab vedotin. Treatment was continued until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, KEYTRUDA was continued for up to 2 years.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5) on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity for up to 6 cycles.

Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

The median age was 69 years (range: 22 to 91); 77% were male; 67% were White, 22% were Asian, 1% were Black or African American, and 10% were unknown or other; 12% were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (49%), 1 (47%), or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer, including 72% with visceral and 22% with liver metastases, and 5% had locally advanced urothelial cancer. Eighty-five percent of patients had urothelial carcinoma (UC) histology including 6% with UC mixed squamous differentiation and 2% with UC mixed other histologic variants. Forty-six percent of patients were considered cisplatin-ineligible and 54% were considered cisplatin-eligible at time of randomization.

The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.

The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients randomized to KEYTRUDA in combination with enfortumab vedotin as compared to platinum-based chemotherapy. Efficacy results were consistent across all stratified patient subgroups.

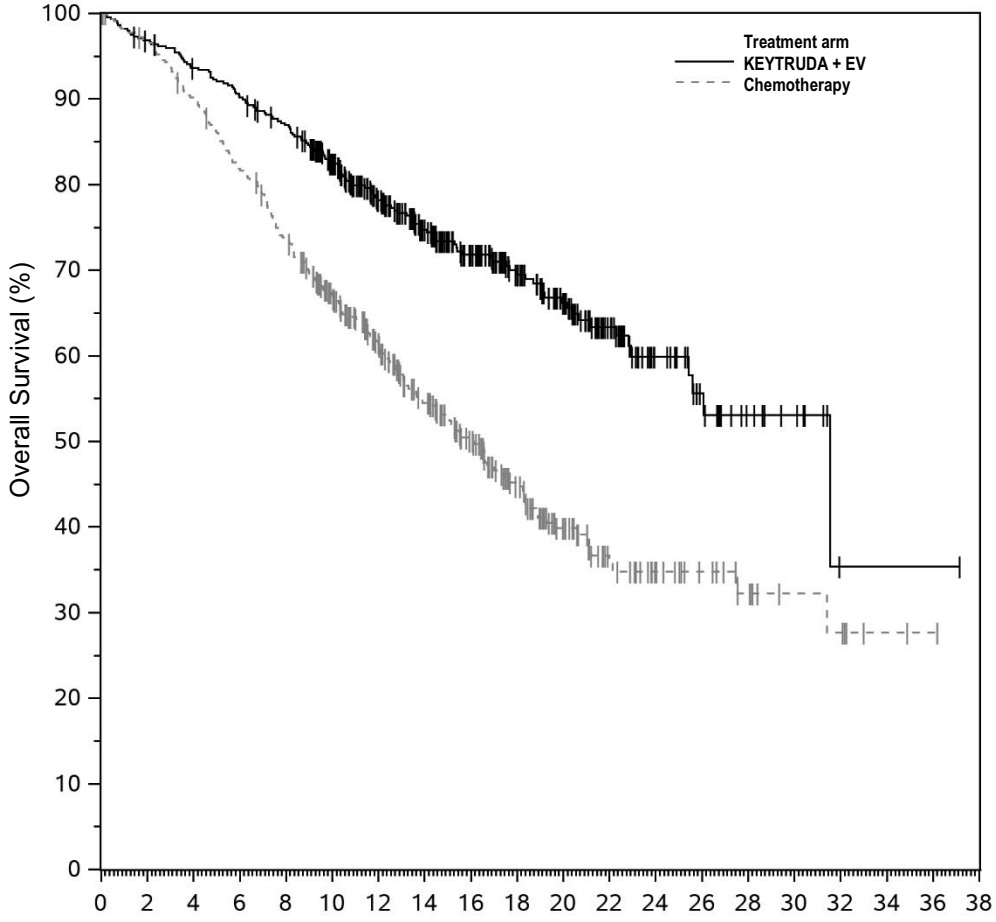
Table 74 and Figures 15 and 16 summarize the efficacy results for KEYNOTE-A39.

Table 74: Efficacy Results in KEYNOTE-A39

Endpoint	**KEYTRUDA 200 mg every 3 weeks in combination with Enfortumab Vedotin n=442**	**Cisplatin or carboplatin with gemcitabine n=444**
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	<0.0001	
Confirmed Objective Response Rate‡		
ORR§ % (95% CI)	68% (63, 72)	44% (40, 49)
p-Value¶	<0.0001	
Complete response	29%	12%
Partial response	39%	32%

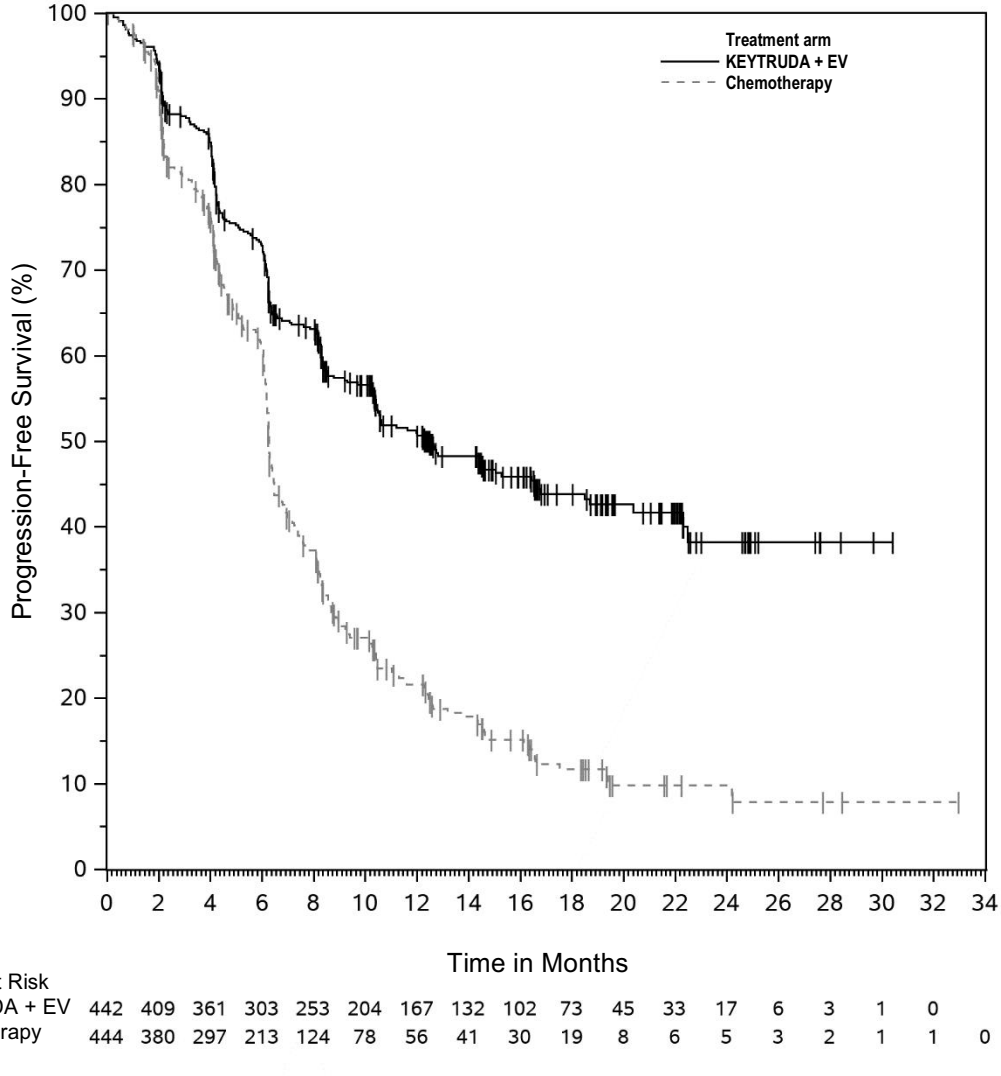
* Based on the stratified Cox proportional hazard regression model
† Two-sided p-Value based on stratified log-rank test
‡ Includes only patients with measurable disease at baseline (n=437 for KEYTRUDA in combination with enfortumab vedotin, n=441 for chemotherapy).
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases
NR = not reached

Figure 15: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



Number at Risk																			
KEYTRUDA + EV	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1	0
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1	0

Figure 16: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39



In Combination with Enfortumab Vedotin for the Treatment of Cisplatin-Ineligible Patients with Urothelial Cancer

The efficacy of KEYTRUDA in combination with enfortumab vedotin was evaluated in KEYNOTE-869 (NCT03288545), an open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) study in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received enfortumab vedotin 1.25 mg/kg as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by KEYTRUDA 200 mg as an IV infusion on Day 1 of a 21-day cycle approximately 30 minutes after enfortumab vedotin. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received KEYTRUDA in combination with enfortumab vedotin. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White, 5% were Black, 4% were Asian and 6% were other, unknown or not reported. Ten percent of patients were Hispanic or Latino. Forty-five

percent of patients had an ECOG performance status of 1 and 15% had an ECOG performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. Reasons for cisplatin-ineligibility included: 60% with baseline creatinine clearance of 30-59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss, and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline, including 22% with liver metastases. Thirty-nine percent of patients had TCC histology; 13% had TCC with squamous differentiation, and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1.

The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range 0.7 to 52.4) and for Cohort K was 14.8 months (range: 0.6 to 26.2).

Efficacy results are presented in Table 75 below.

Table 75: Efficacy Results in KEYNOTE-869, Combined Dose Escalation Cohort, Cohort A, and Cohort K

Endpoint	KEYTRUDA in combination with Enfortumab Vedotin n=121
Confirmed ORR (95% CI)	68% (58.7, 76.0)
Complete response rate	12%
Partial response rate	55%

The median duration of response for the dose escalation cohort + Cohort A was 22.1 months (range: 1.0+ to 46.3+) and for Cohort K was not reached (range: 1.2 to 24.1+).

Platinum-Ineligible Patients with Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who had one or more comorbidities, including patients who were not eligible for any platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 74 years; 77% male; and 89% White. Eighty-seven percent had M1 disease, and 13% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Fifty percent of patients had baseline creatinine clearance of <60 mL/min, 32% had ECOG PS of 2, 9% had ECOG PS of 2 and baseline creatinine clearance of <60 mL/min, and 9% had one or more of Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss. Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

The median follow-up time for 370 patients treated with KEYTRUDA was 11.4 months (range 0.1 to 63.8 months). Efficacy results are summarized in Table 76.

Table 76: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks
	All Subjects n=370
Objective Response Rate	
ORR (95% CI)	29% (24, 34)
Complete response rate	10%
Partial response rate	20%
Duration of Response	
Median in months (range)	33.4 (1.4+, 60.7+)

\+ Denotes ongoing response

Platinum-Eligible Patients with Previously Untreated Urothelial Carcinoma

The efficacy of KEYTRUDA for the first-line treatment of platinum-eligible patients with locally advanced or metastatic urothelial carcinoma was investigated in KEYNOTE-361 (NCT02853305), a multicenter, randomized, open-label, active-controlled study in 1010 previously untreated patients. The safety and efficacy of KEYTRUDA in combination with platinum-based chemotherapy for previously untreated patients with locally advanced or metastatic urothelial carcinoma has not been established.

The study compared KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. Among the patients receiving KEYTRUDA plus platinum-based chemotherapy, 44% received cisplatin and 56% received carboplatin.

The study did not meet its major efficacy outcome measures of improved PFS or OS in the KEYTRUDA plus chemotherapy arm compared to the chemotherapy-alone arm. Additional efficacy endpoints, including improvement of OS in the KEYTRUDA monotherapy arm, could not be formally tested.

Previously Treated Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-045 (NCT02256436), a multicenter, randomized (1:1), active-controlled trial in 542 patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=90), docetaxel 75 mg/m^2 (n=92), or vinflunine 320 mg/m^2 (n=90). Treatment continued until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age of 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG PS of 0 and 56% ECOG PS of 1; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumor in the lower tract and 14% had a primary tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

The study demonstrated statistically significant improvements in OS and ORR for patients randomized to KEYTRUDA as compared to chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. The median follow-up time for this trial was 9.0 months (range: 0.2 to 20.8 months). Table 77 and Figure 17 summarize the efficacy results for KEYNOTE-045.

Table 77: Efficacy Results in KEYNOTE-045

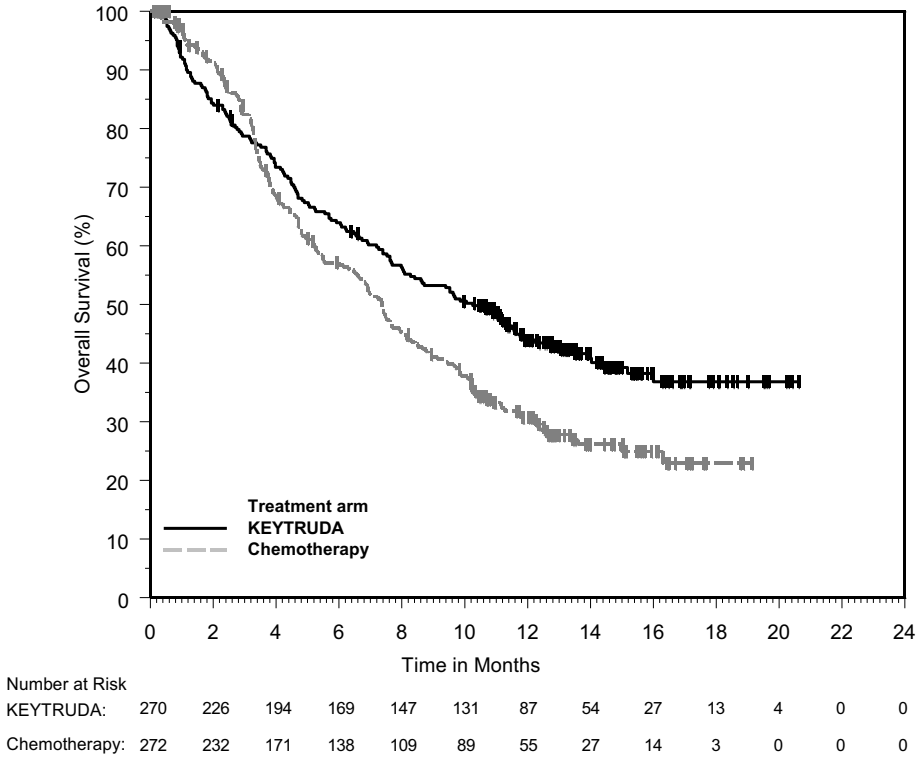
	KEYTRUDA 200 mg every 3 weeks n=270	**Chemotherapy n=272**
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value (stratified log-rank)	0.833	
Objective Response Rate		
ORR (95% CI)	21% (16, 27)	11% (8, 16)
Complete response rate	7%	3%
Partial response rate	14%	8%
p-Value (Miettinen-Nurminen)	0.002	
Median duration of response in months (range)	NR (1.6+, 15.6+)	4.3 (1.4+, 15.4+)

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

\+ Denotes ongoing response

NR = not reached

Figure 17: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-057 (NCT02625961), a multicenter, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC was defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy was defined as administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all patients had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, or autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumor status was performed every 12 weeks for two years and then every 24 weeks for three years, and patients without disease progression could be treated for up to 24 months. The major efficacy outcome measures were complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response.

The study population characteristics were: median age of 73 years (range: 44 to 92); 44% age ≥75; 84% male; 67% White; and 73% and 27% with an ECOG performance status of 0 or 1, respectively. Tumor pattern at study entry was CIS with T1 (13%), CIS with high grade TA (25%), and CIS (63%). Baseline high-risk NMIBC disease status was 27% persistent and 73% recurrent. The median number of prior instillations of BCG was 12.

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarized in Table 78.

Table 78: Efficacy Results in KEYNOTE-057

Endpoint	KEYTRUDA 200 mg every 3 weeks n=96
Complete Response Rate (95% CI)	41% (31, 51)
Duration of Response*	
Median in months (range)	16.2 (0.0+, 30.4+)
% (n) with duration ≥12 months	46% (18)

* Based on patients (n=39) that achieved a complete response; reflects period from the time complete response was achieved

\+ Denotes ongoing response

14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.

- KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.
- KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively

enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).

- KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.

Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051.

In KEYNOTE-164 and KEYNOTE-158, the study population characteristics were median age of 60 years, 36% age 65 or older; 44% male; 78% White, 14% Asian, 4% American Indian or Alaska Native, and 3% Black; and 45% ECOG PS of 0 and 55% ECOG PS of 1. Ninety-two percent of patients had metastatic disease and 4% had locally advanced, unresectable disease. Thirty-seven percent of patients received one prior line of therapy and 61% received two or more prior lines of therapy.

In KEYNOTE-051, the study population characteristics were median age of 11 years (range: 3 to 16); 71% female; 86% White and 14% Asian; and 57% had a Lansky/Karnofsky Score of 100. Seventy-one percent of patients had Stage IV and 14% had Stage III disease. Fifty-seven percent of patients received one prior line of therapy and 29% received two prior lines of therapy.

Discordant results were observed between local MSI-H or dMMR tests and central testing among patients enrolled in Cohort K of KEYNOTE-158. Among 104 tumor samples that were MSI-H or dMMR by local testing and also tested using the FoundationOne®CDx (F1CDx) test, 59 (56.7%) were MSI-H and 45 (43.3%) were not MSI-H. Among 169 tumor samples that were MSI-H or dMMR by local testing and also tested using the VENTANA MMR RxDx Panel, 105 (62.1%) were dMMR and 64 (37.9%) were pMMR.

Efficacy results are summarized in Tables 79 and 80.

Table 79: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	KEYTRUDA n=504*
Objective Response Rate	
ORR (95% CI)†	33.3% (29.2, 37.6)
Complete response rate	10.3%
Partial response rate	23.0%
Duration of Response	n=168
Median in months (range)	63.2 (1.9+, 63.9+)
% with duration ≥12 months	77%
% with duration ≥36 months	39%

* Median follow-up time of 20.1 months (range 0.1 to 71.4 months)

† Of the 7 pediatric patients from KEYNOTE-051, 1 patient had a radiographic complete response after initial growth of their tumor but is not reflected in the results.

\+ Denotes ongoing response

Table 80: Response by Tumor Type

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
CRC	124	42 (34%)	(26%, 43%)	(4.4, 58.5+)
Non-CRC*	380	126 (33%)	(28%, 38%)	(1.9+, 63.9+)
Endometrial cancer	94	47 (50%)	(40%, 61%)	(2.9, 63.2)
Gastric or GE junction cancer	51	20 (39%)	(26%, 54%)	(1.9+, 63.0+)
Small intestinal cancer	27	16 (59%)	(39%, 78%)	(3.7+, 57.3+)
Brain cancer	27†	1 (4%)‡	(0%, 19%)	18.9
Ovarian cancer	25	8 (32%)	(15%, 54%)	(4.2, 56.6+)
Biliary cancer	22	9 (41%)	(21%, 64%)	(6.2, 49.0+)
Pancreatic cancer	22	4 (18%)	(5%, 40%)	(8.1, 24.3+)
Sarcoma	14	3 (21%)	(5%, 51%)	(35.4+, 57.2+)
Breast cancer	13	1 (8%)	(0%,36%)	24.3+
Other§	13	4 (31%)	(9%, 61%)	(6.2+, 32.3+)
Cervical cancer	11	1 (9%)	(0%, 41%)	63.9+
Neuroendocrine cancer	11	1 (9%)	(0%, 41%)	13.3
Prostate cancer	8	1 (13%)	(0%, 53%)	24.5+
Adrenocortical cancer	7	1 (14%)	(0%, 58%)	4.2
Mesothelioma	7	0 (0%)	(0%, 41%)	
Thyroid cancer	7	1 (14%)	(0%, 58%)	8.2
Small cell lung cancer	6	2 (33%)	(4%, 78%)	(20.0, 47.5)
Bladder cancer	6	3 (50%)	(12%, 88%)	(35.6+, 57.5+)
Salivary cancer	5	2 (40%)	(5%, 85%)	(42.6+, 57.8+)
Renal cell cancer	4	1 (25%)	(0%, 81%)	22.0

* Results include patients in Cohort K of KEYNOTE-158 that were later determined to be pMMR or not MSI-H by central testing

† Includes 6 pediatric patients with brain cancer

‡ In addition to the 1 adult responder, 1 pediatric patient had a radiographic complete response after initial growth of their tumor.

§ Includes tumor type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1). Includes 1 pediatric patient with abdominal adenocarcinoma.

\+ Denotes ongoing response

Exploratory analysis by TMB

In an exploratory analysis performed in 138 patients (Cohort K of KEYNOTE-158) who were tested retrospectively for tumor mutation burden (TMB) using an FDA-approved test, 45 (33%) had tumors with TMB score of <10 mut/Mb; ORR in these 45 patients was 6.7% (95% CI: 1.4, 18.3). Among the 45 patients with TMB score of <10 mut/Mb, 39 of the patients were not MSI-H/dMMR when tested using an FDA-approved test.

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The main efficacy outcome measures were PFS (as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Additional efficacy outcome measures were ORR and DoR.

A total of 307 patients were enrolled and randomized to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1; and 27% received prior adjuvant or neoadjuvant chemotherapy. Among 154 patients randomized to receive chemotherapy,143 received chemotherapy per the protocol. Of the 143 patients, 56% received mFOLFOX6, 44% received FOLFIRI, 70% received bevacizumab plus mFOLFOX6 or FOLFIRI, and 11% received cetuximab plus mFOLFOX6 or FOLFIRI.

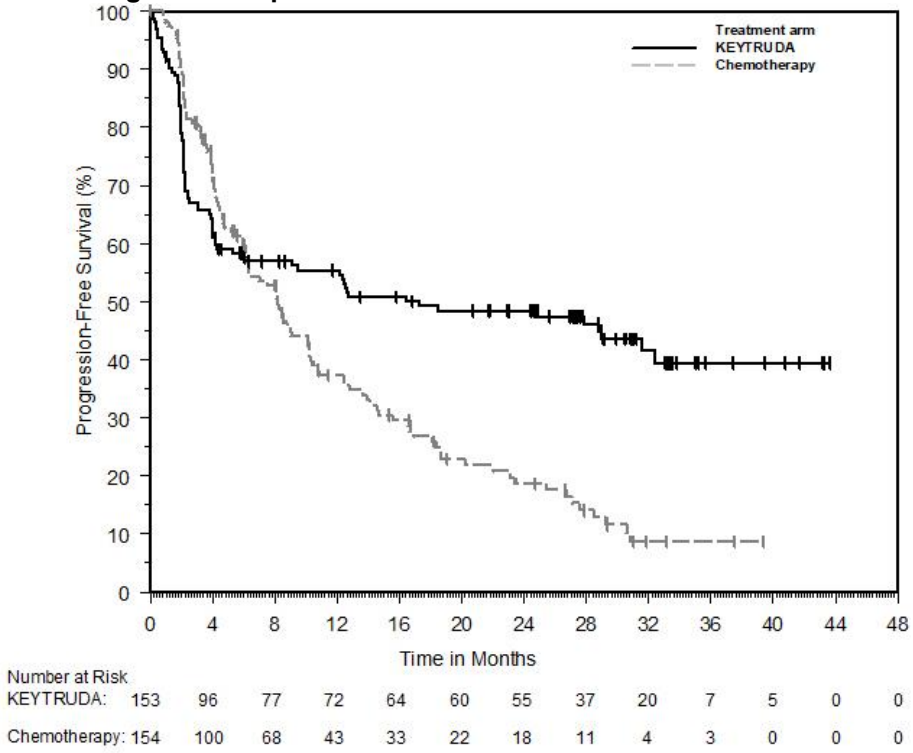
The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis. Sixty percent of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time at the final analysis was 38.1 months (range: 0.2 to 58.7 months). Table 81 and Figure 18 summarize the key efficacy measures for KEYNOTE-177.

Table 81: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=153**	**Chemotherapy n=154**
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
OS‡		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio* (95% CI)	0.74 (0.53, 1.03)	
p-Value§	0.0718	
Objective Response Rate¶		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Duration of Response¶,#		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 monthsᵇ	75%	37%
% with duration ≥24 monthsᵇ	43%	18%

* Based on Cox regression model
† Two-sided p-Value based on log-rank test (compared to a significance level of 0.0234)
‡ Final OS analysis
§ Two-sided p-Value based on log-rank test (compared to a significance level of 0.0492)
¶ Based on confirmed response by BICR review
\# Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
ᵇ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

Figure 18: Kaplan-Meier Curve for PFS in KEYNOTE-177



14.9 Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811 (NCT03615326), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS $\geq$1 or CPS <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX). KEYTRUDA was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. In an interim efficacy analysis, the major outcome measures assessed were ORR and DoR by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

At the time of the interim analysis, ORR and DoR were assessed in the first 264 patients randomized. Among the 264 patients, the population characteristics were: median age of 62 years (range: 19 to 84), 41% age 65 or older; 82% male; 63% White, 31% Asian, and 0.8% Black; 47% ECOG PS of 0 and 53% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Ninety-one percent (n=240) had tumors that were not MSI-H, 1% (n=2) had tumors that were MSI-H, and in 8% (n=22) the status was not known. Eighty-seven percent of patients received CAPOX.

A statistically significant improvement in ORR was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. Efficacy results are summarized in Table 82.

Table 82: Efficacy Results for KEYNOTE-811

Endpoint	**KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=133**	**Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=131**
Objective Response Rate		
ORR* (95% CI)	74% (66, 82)	52% (43, 61)
Complete response rate	11%	3.1%
Partial response rate	63%	49%
p-Value†	<0.0001	
Duration of Response	n=99	n=68
Median in months (range)	10.6 (1.1+, 16.5+)	9.5 (1.4+, 15.4+)
% with duration ≥6 months‡	65%	53%

* Response: Best objective response as confirmed complete response or partial response
† p-Value based on stratified Miettinen and Nurminen method (compared to an alpha boundary of 0.002)
‡ Based on observed duration of response
\+ Denotes ongoing response

In a pre-specified subgroup analysis of ORR based on PD-L1 status, the ORR in patients with PD-L1-positive disease (CPS ≥1) was 76% (95% CI: 67, 83) in the pembrolizumab arm (n=117) versus 51% (95% CI: 41, 60) in the control arm (n=112). In patients with tumors that were PD-L1 CPS<1, the ORR was 63% (95% CI: 35, 85) in the pembrolizumab arm (n=16) versus 58% (95% CI: 34, 80) in the control arm (n=19).

In a subsequent interim analysis of pre-specified subgroups based on PD-L1 status in the full study population (n=698), the HR for PFS and OS in patients with PD-L1 CPS<1 (N=104) was 1.03 (95% CI: 0.65, 1.64) and 1.41 (95% CI: 0.90, 2.20), respectively.

First-line Treatment of Locally Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma

The efficacy of KEYTRUDA in combination with fluoropyrimidine- and platinum-containing chemotherapy was investigated in KEYNOTE-859 (NCT03675737), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or GEJ adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥1 or CPS <1), chemotherapy regimen (FP or CAPOX), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; treatment was administered prior to chemotherapy on Day 1 of each cycle:

- KEYTRUDA 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Platinum agents could be administered for 6 or more cycles following local guidelines. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. The major efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DoR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The population characteristics were: median age of 62 years (range: 21 to 86), 39% age 65 or older; 68% male and 32% female; 55% White, 34% Asian, 4.6% Multiple, 4.2% American Indian or Alaskan Native, 1.3% Black, and 0.2% Native Hawaiian or other Pacific Islander; 76% Not Hispanic or Latino and 21% Hispanic or Latino; 37% ECOG PS of 0 and 63% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Seventy-eight percent had tumors that expressed PD-L1 with a CPS ≥1 and 5% (n=74) had tumors that were MSI-H. Eighty-six percent of patients received CAPOX.

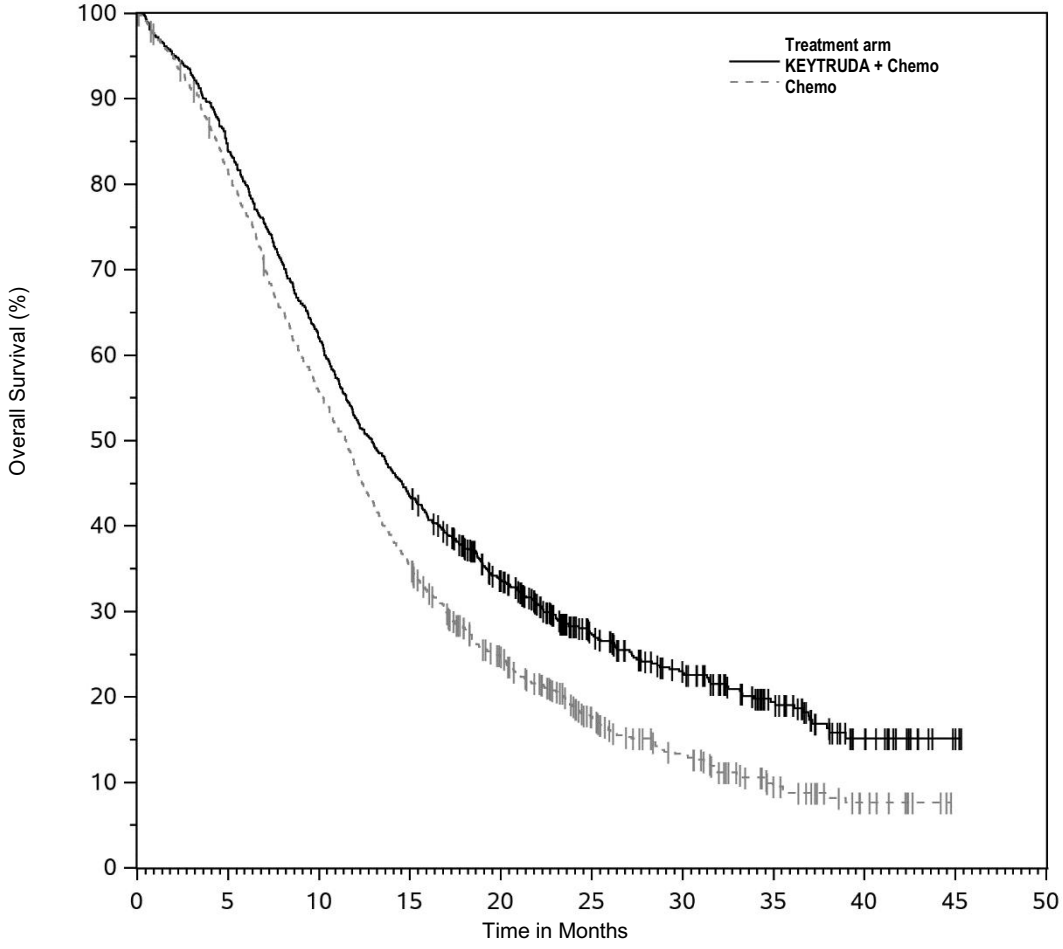
A statistically significant improvement in OS, PFS, and ORR was demonstrated in patients randomized to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy at the time of a pre-specified interim analysis of OS. Efficacy results are summarized in Table 83 and Figures 19 and 20.

Table 83: Efficacy Results* for KEYNOTE-859

Endpoint	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=790	Placebo and FP or CAPOX n=789	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=618	Placebo and FP or CAPOX n=617	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=279	Placebo and FP or CAPOX n=272
	All Patients		CPS≥1		CPS≥10	
OS						
Number (%) of patients with event	603 (76)	666 (84)	464 (75)	526 (85)	188 (67)	226 (83)
Median in months (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
Hazard ratio† (95% CI)	0.78 (0.70, 0.87)		0.74 (0.65, 0.84)		0.65 (0.53, 0.79)	
p-Value (stratified log-rank)‡	<0.0001		<0.0001		<0.0001	
PFS						
Number (%) of patients with event	572 (72)	608 (77)	443 (72%)	483 (78%)	190 (68)	210 (77)
Median in months (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
Hazard ratio† (95% CI)	0.76 (0.67, 0.85)		0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
p-Value (stratified log-rank)‡	<0.0001		<0.0001		<0.0001	
Objective Response Rate						
ORR§ (95% CI)	51% (48, 55)	42% (38, 45)	52% (48, 56)	43% (39, 47)	61% (55, 66)	43% (37, 49)
Complete response rate	9%	6%	10%	6%	13%	5%
Partial response rate	42%	36%	42%	37%	48%	38%
p-Value¶	<0.0001		0.0004		<0.0001	
Duration of Response	n=405	n=331	n=322	n=263	n=169	n=117
Median in months# (95% CI)	8.0 (7.0, 9.7)	5.7 (5.5, 6.9)	8.3 (7.0, 10.9)	5.6 (5.4, 6.9)	10.9 (8.0, 13.8)	5.8 (5.3, 7.0)
Range in months	1.2+, 41.5+	1.3+, 34.7+	1.2+, 41.5+	1.3+, 34.2+	1.2+, 41.5+	1.4+, 31.2+

* Based on a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ One-sided p-Value based on stratified Miettinen & Nurminen method
# Based on Kaplan-Meier estimates
\+ Denotes ongoing response

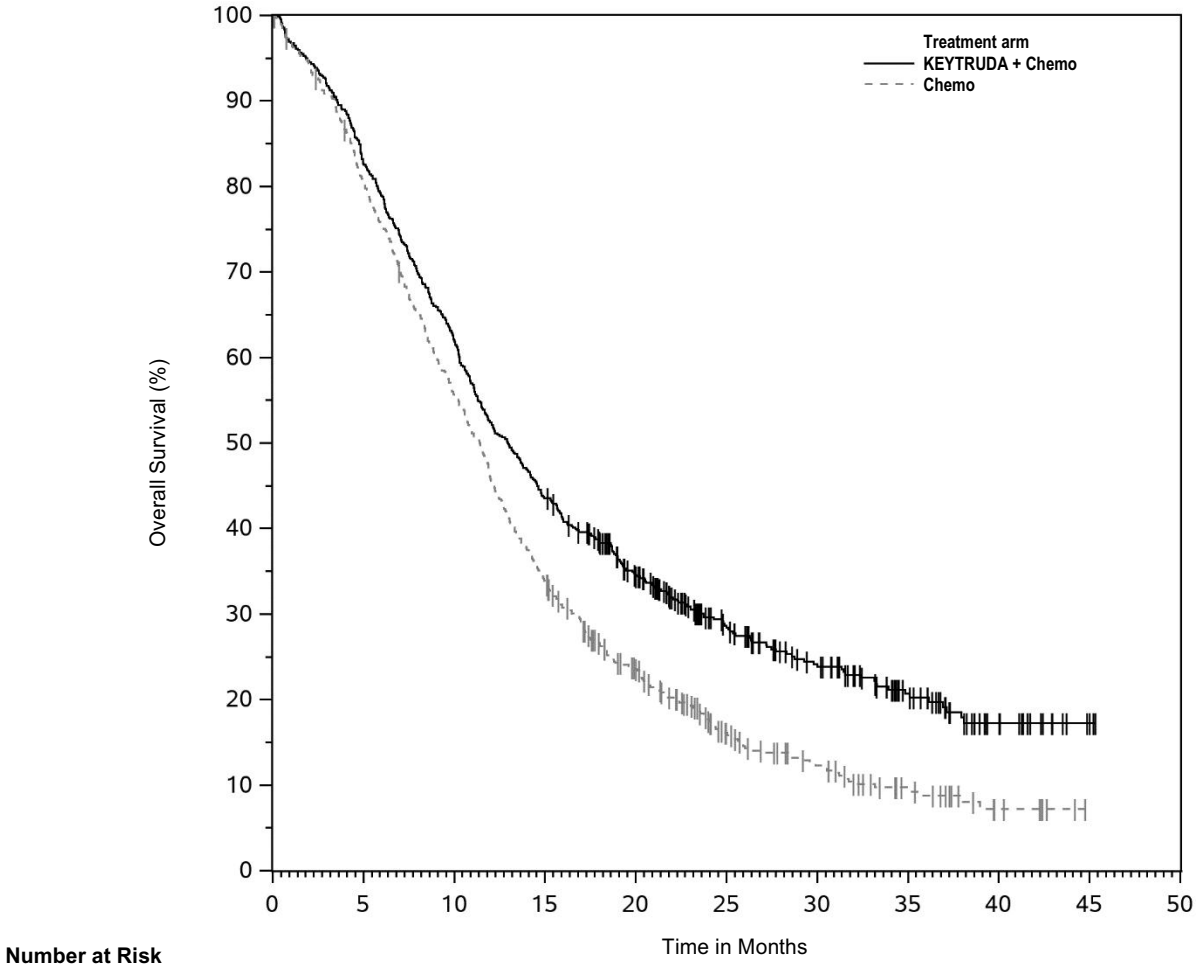
Figure 19: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859



Number at Risk

KEYTRUDA + Chemo	790	663	490	343	240	143	95	55	19	3	0
Chemo	789	636	434	274	169	95	58	26	10	0	0

Figure 20: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS≥1)



In an exploratory subgroup analysis in patients with PD-L1 CPS<1 (n=344) at the time of the pre-specified interim analysis of OS, the median OS was 12.7 months (95% CI: 11.4, 15.0) for the KEYTRUDA arm and 12.2 months (95% CI: 9.5, 14.0) for the placebo arm, with a HR of 0.92 (95% CI: 0.73, 1.17).

14.10 Esophageal Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal/Gastroesophageal Junction Cancer

KEYNOTE-590

The efficacy of KEYTRUDA was investigated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation. PD-L1 status was centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or who received

prior systemic therapy in the locally advanced or metastatic setting were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients could be treated with KEYTRUDA for up to 24 months in the absence of disease progression. The major efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). The study pre-specified analyses of OS and PFS based on squamous cell histology, CPS ≥10, and in all patients. Additional efficacy outcome measures were ORR and DoR, according to modified RECIST v1.1, as assessed by the investigator.

The study population characteristics were: median age of 63 years (range: 27 to 94), 43% age 65 or older; 83% male; 37% White, 53% Asian, and 1% Black; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-three percent had a tumor histology of squamous cell carcinoma, and 27% had adenocarcinoma.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with chemotherapy, compared to chemotherapy.

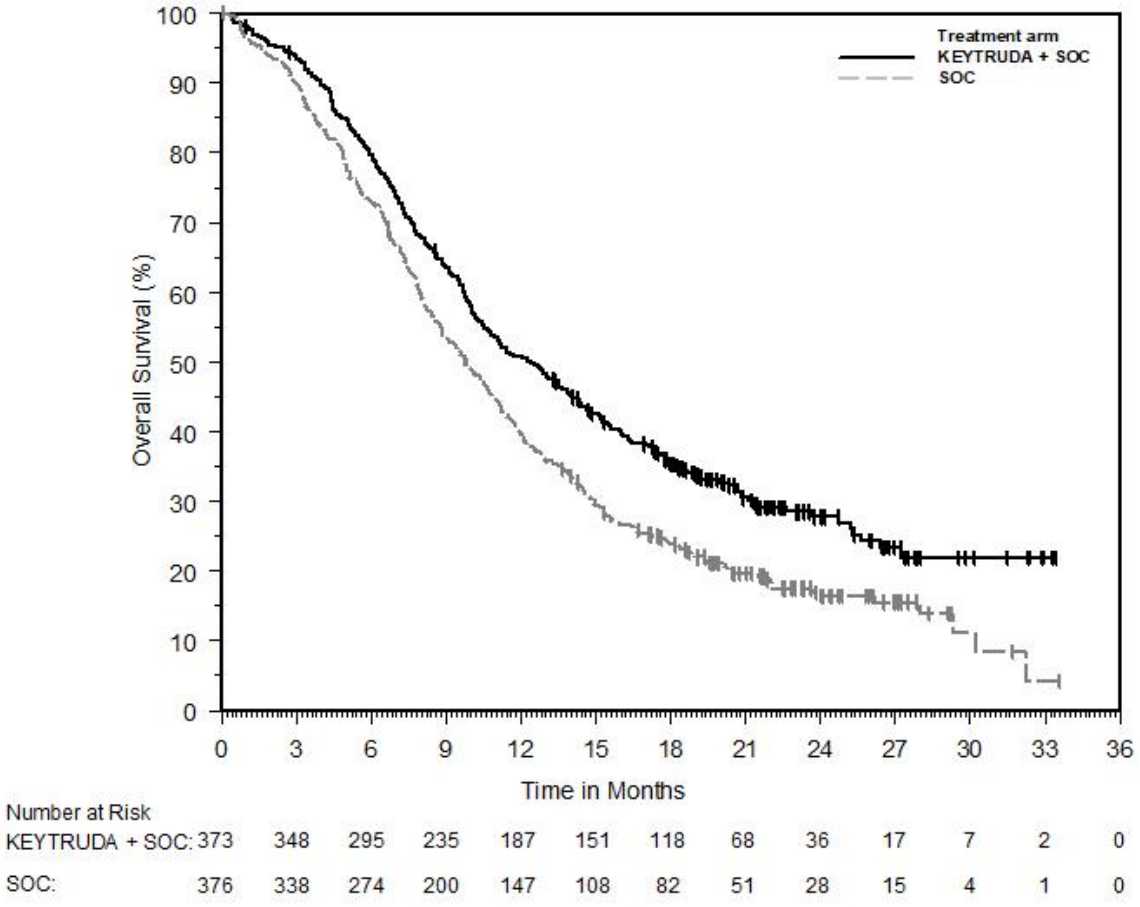
Table 84 and Figure 21 summarize the efficacy results for KEYNOTE-590 in all patients.

Table 84: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Esophageal Cancer in KEYNOTE-590

Endpoint	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=373	Placebo Cisplatin FU n=376
OS		
Number (%) of events	262 (70)	309 (82)
Median in months (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Hazard ratio* (95% CI)	0.73 (0.62, 0.86)	
p-Value†	<0.0001	
PFS		
Number of events (%)	297 (80)	333 (89)
Median in months (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Hazard ratio* (95% CI)	0.65 (0.55, 0.76)	
p-Value†	<0.0001	
Objective Response Rate		
ORR, %‡ (95% CI)	45 (40, 50)	29 (25, 34)
Number (%) of complete responses	24 (6)	9 (2.4)
Number (%) of partial responses	144 (39)	101 (27)
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	8.3 (1.2+, 31.0+)	6.0 (1.5+, 25.0+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ Confirmed complete response or partial response
§ Based on the stratified Miettinen and Nurminen method

Figure 21: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590



In a pre-specified formal test of OS in patients with PD-L1 CPS ≥ 10 (n=383), the median was 13.5 months (95% CI: 11.1, 15.6) for the KEYTRUDA arm and 9.4 months (95% CI: 8.0, 10.7) for the placebo arm, with a HR of 0.62 (95% CI: 0.49, 0.78; p-Value < 0.0001). In an exploratory analysis, in patients with PD-L1 CPS < 10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the KEYTRUDA arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with a HR of 0.86 (95% CI: 0.68, 1.10).

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer

KEYNOTE-181

The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either KEYTRUDA 200 mg every 3 weeks or investigator's choice of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (esophageal squamous cell carcinoma [ESCC] vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with KEYTRUDA or chemotherapy continued

until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measure was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. Additional efficacy outcome measures were PFS, ORR, and DoR, according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to KEYTRUDA (n=314) or investigator's treatment of choice (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 patients were randomized to KEYTRUDA and 82 patients to investigator's treatment of choice [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)]. The baseline characteristics of these 167 patients were: median age of 65 years (range: 33 to 80), 51% age 65 or older; 84% male; 32% White and 68% Asian; 38% had an ECOG PS of 0 and 62% had an ECOG PS of 1. Ninety percent had M1 disease and 10% had M0 disease. Prior to enrollment, 99% of patients had received platinum-based treatment and 84% had also received treatment with a fluoropyrimidine. Thirty-three percent of patients received prior treatment with a taxane.

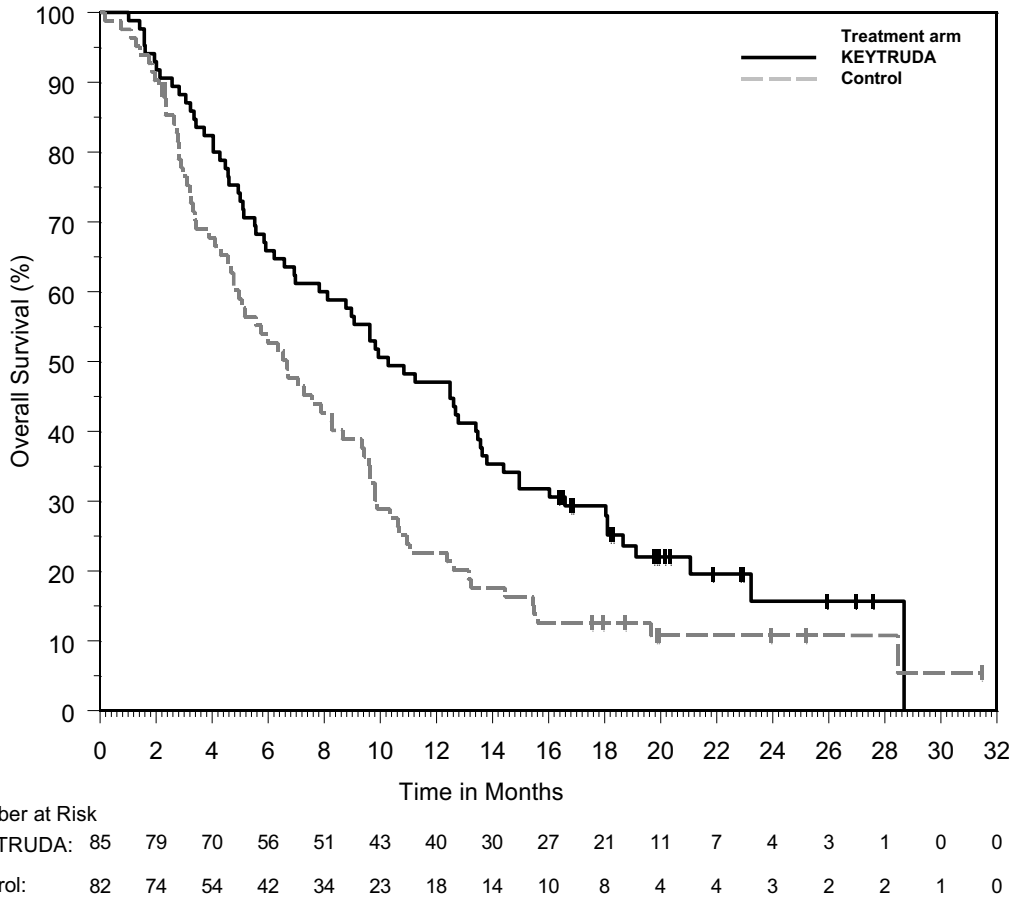
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 85 and Figure 22 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 85: Efficacy Results in Patients with Recurrent or Metastatic ESCC (CPS ≥10) in KEYNOTE-181

Endpoint	KEYTRUDA 200 mg every 3 weeks n=85	Chemotherapy n=82
OS		
Number (%) of patients with event	68 (80%)	72 (88%)
Median in months (95% CI)	10.3 (7.0, 13.5)	6.7 (4.8, 8.6)
Hazard ratio* (95% CI)	0.64 (0.46, 0.90)	
PFS		
Number (%) of patients with event	76 (89%)	76 (93%)
Median in months (95% CI)	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
Hazard ratio* (95% CI)	0.66 (0.48, 0.92)	
Objective Response Rate		
ORR (95% CI)	22 (14, 33)	7 (3, 15)
Number (%) of complete responses	4 (5)	1 (1)
Number (%) of partial responses	15 (18)	5 (6)
Median duration of response in months (range)	9.3 (2.1+, 18.8+)	7.7 (4.3, 16.8+)

* Based on the Cox regression model stratified by geographic region (Asia vs. ex-Asia)

Figure 22: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS ≥10)



KEYNOTE-180

The efficacy of KEYTRUDA was investigated in KEYNOTE-180 (NCT02559687), a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. With the exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181.

The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The baseline characteristics of these 35 patients were: median age of 65 years (range: 47 to 81), 51% age 65 or older; 71% male; 26% White and 69% Asian; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. One hundred percent had M1 disease.

The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8, 37). Among the 7 responding patients, the DoR ranged from 4.2 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer.

14.11 Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The efficacy of KEYTRUDA in combination with CRT (cisplatin and external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18 (NCT04221945), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1060 patients with cervical

cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 596 patients with FIGO 2014 Stage III-IVA (tumor involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease, and 462 patients with FIGO 2014 Stage IB2-IIB (tumor lesions >4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) with node-positive disease; two patients had FIGO 2014 Stage IVB disease. Randomization was stratified by planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. FIGO 2014 Stage III-IVA), and planned total radiotherapy dose (EBRT + brachytherapy dose of <70 Gy vs. ≥70 Gy as per equivalent dose [EQD2]).

Patients were randomized (1:1) to one of two treatment arms:

- KEYTRUDA 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by KEYTRUDA 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity.

Assessment of tumor status was performed every 12 weeks from completion of CRT for the first two years, followed by every 24 weeks in year 3, and then annually. The major efficacy outcome measures were PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or histopathologic confirmation, and OS.

Among the 596 patients with FIGO 2014 Stage III-IVA disease, the baseline characteristics were: median age of 52 years (range: 22 to 87), 17% age 65 or older; 36% White, 34% Asian, 1% Black; 38% Hispanic or Latino; 68% ECOG PS 0 and 32% ECOG PS 1; 93% with CPS ≥1; 70% had positive pelvic and/or positive para-aortic lymph node(s) and 30% had neither positive pelvic nor para-aortic lymph node(s); 83% had squamous cell carcinoma and 17% had non-squamous histology. Regarding radiation, 85% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 7 to 114).

The trial demonstrated a statistically significant improvement in PFS in the overall population. In an exploratory subgroup analysis for the 462 patients (44%) with FIGO 2014 Stage IB2-IIB disease, the PFS HR estimate was 0.91 (95% CI: 0.63, 1.31), indicating that the PFS improvement in the overall population was primarily attributed to the results seen in the subgroup of patients with FIGO 2014 Stage III-IVA disease. OS data were not mature at the time of PFS analysis, with 10% deaths in the overall population.

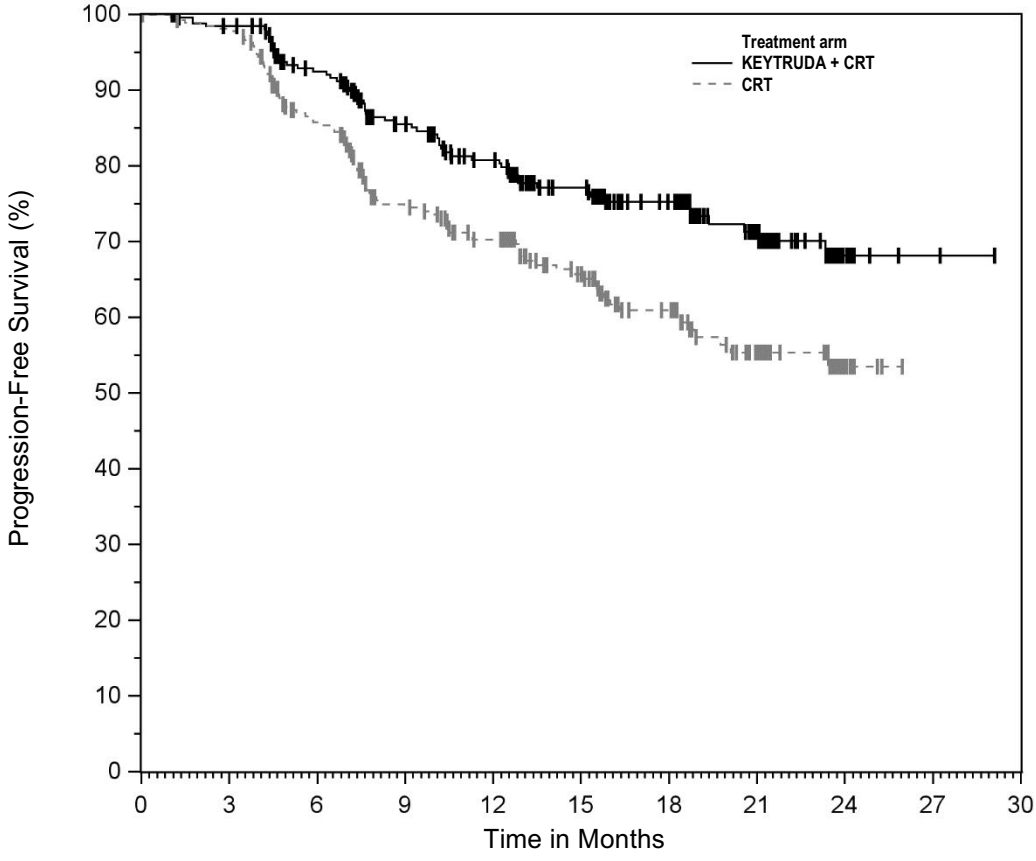
The efficacy results in the exploratory subgroup analysis of 596 patients with FIGO 2014 Stage III-IVA disease are summarized in Table 86 and Figure 23.

Table 86: Efficacy Results in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)

Endpoint	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=293	Placebo with CRT n=303
PFS by Investigator		
Number of patients with event (%)	61 (21%)	94 (31%)
Median in months (95% CI)	NR (NR, NR)	NR (18.8, NR)
12-month PFS rate (95% CI)	81% (75, 85)	70% (64, 76)
Hazard ratio* (95% CI)	0.59 (0.43, 0.82)	

* Based on the unstratified Cox proportional hazard model
CRT = Chemoradiotherapy
NR = not reached

Figure 23: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)



Number at Risk											
KEYTRUDA + CRT	293	254	223	186	163	129	96	62	11	2	0
CRT	303	261	209	163	142	109	78	46	8	0	0

Persistent, Recurrent, or Metastatic Cervical Cancer

The efficacy of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826 (NCT03635567), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumor PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10). Patients were randomized (1:1) to one of the two treatment groups:

- Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomization:

1. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2

2. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 9 weeks for the first year, followed by every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by investigator.

Of the 617 enrolled patients, 548 patients (89%) had tumors expressing PD-L1 with a CPS ≥1. Among these 548 enrolled patients with tumors expressing PD-L1, 273 patients were randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were randomized to placebo in combination with chemotherapy with or without bevacizumab. Sixty-three percent of the 548 patients received bevacizumab as part of study treatment. The baseline characteristics of the 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, 6% American Indian or Alaska Native, and 1% Black; 37% Hispanic or Latino; 56% ECOG performance status 0 and 43% ECOG performance status 1. Seventy-five percent had squamous cell carcinoma, 21% adenocarcinoma, and 5% adenosquamous histology, and 32% of patients had metastatic disease at diagnosis. At study entry, 21% of patients had metastatic disease only and 79% had persistent or recurrent disease with or without distant metastases, of whom 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

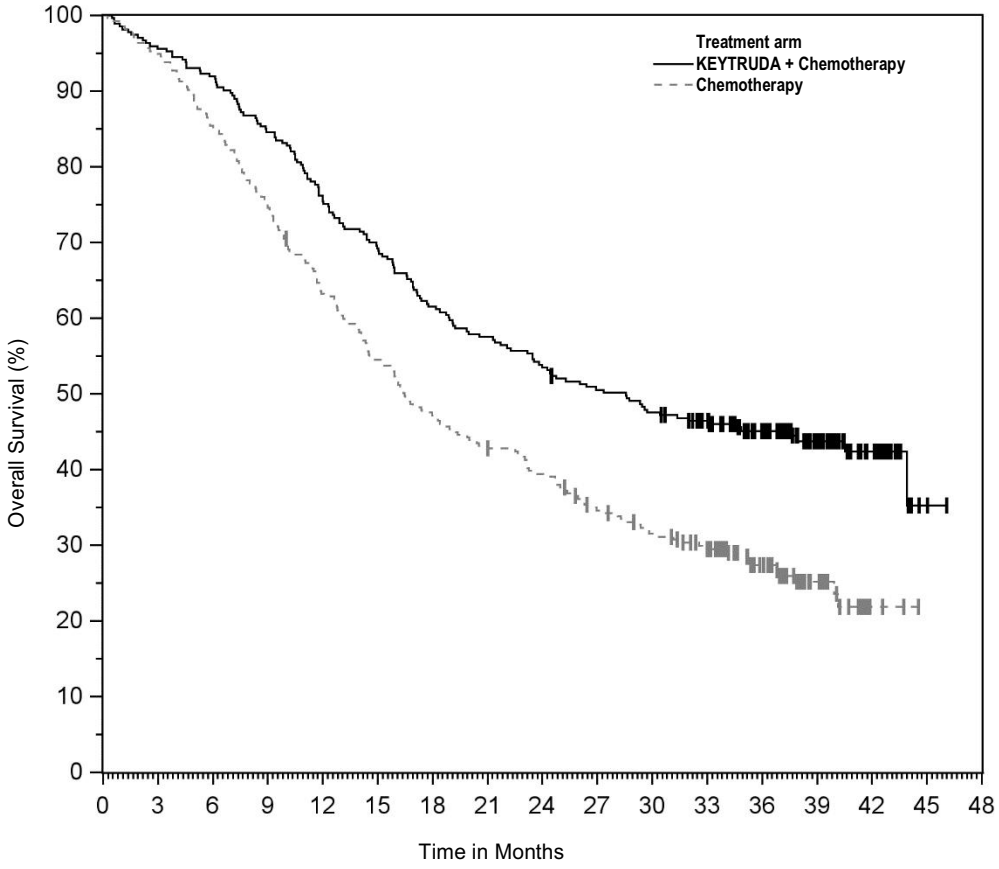
A statistically significant improvement in OS and PFS was demonstrated in patients randomized to receive KEYTRUDA compared with patients randomized to receive placebo. An updated OS analysis was conducted at the time of final analysis when 354 deaths in the CPS ≥1 population were observed. Table 87 and Figure 24 summarize the key efficacy measures for KEYNOTE-826 for patients with tumors expressing PD-L1 (CPS ≥1).

Table 87: Efficacy Results in Patients with Persistent, Recurrent, or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-826

Endpoint	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=273	Placebo and chemotherapy* with or without bevacizumab n=275
OS		
Number of patients with event (%)	118 (43.2)	154 (56.0)
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
Hazard ratio† (95% CI)	0.64 (0.50, 0.81)	
p-Value‡	0.0001	
Updated OS		
Number of patients with event (%)	153 (56.0%)	201 (73.1%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
PFS		
Number of patients with event (%)	157 (57.5)	198 (72.0)
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio† (95% CI)	0.62 (0.50, 0.77)	
p-Value§	< 0.0001	
Objective Response Rate		
ORR¶ (95% CI)	68% (62, 74)	50% (44, 56)
Complete response rate	23%	13%
Partial response rate	45%	37%
Duration of Response		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0055 for this interim analysis (with 72% of the planned number of events for final analysis)
§ p-Value (one-sided) is compared with the allocated alpha of 0.0014 for this interim analysis (with 82% of the planned number of events for final analysis)
¶ Response: Best objective response as confirmed complete response or partial response
\+ Denotes ongoing response
NR = not reached

Figure 24: Kaplan-Meier Curve for Overall Survival in KEYNOTE-826 (CPS ≥1)*,†



Number at Risk

KEYTRUDA + Chemotherapy	273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
Chemotherapy	275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

*Treatment arms include KEYTRUDA plus chemotherapy, with or without bevacizumab, versus placebo plus chemotherapy, with or without bevacizumab.
†Based on the protocol-specified final OS analysis

Previously Treated Recurrent or Metastatic Cervical Cancer

The efficacy of KEYTRUDA was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

Among the 98 patients in Cohort E, 77 (79%) had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy in the metastatic setting. PD-L1 status was determined using the IHC 22C3 pharmDx kit. The baseline characteristics of these 77 patients were: median age of 45 years (range: 27 to 75); 81% White, 14% Asian, and 3% Black; 32% ECOG PS of 0 and 68% ECOG PS of 1; 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology;

95% had M1 disease and 5% had recurrent disease; and 35% had one and 65% had two or more prior lines of therapy in the recurrent or metastatic setting.

No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 88 for patients with PD-L1 expression (CPS ≥1).

Table 88: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

Endpoint	KEYTRUDA 200 mg every 3 weeks n=77*
Objective Response Rate	
ORR (95% CI)	14.3% (7.4, 24.1)
Complete response rate	2.6%
Partial response rate	11.7%
Duration of Response	
Median in months (range)	NR (4.1, 18.6+)†
% with duration ≥6 months	91%

* Median follow-up time of 11.7 months (range 0.6 to 22.7 months)
† Based on patients (n=11) with a response by independent review
\+ Denotes ongoing response
NR = not reached

14.12 Hepatocellular Carcinoma

Previously Treated HCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-394 (NCT03062358), a multicenter, randomized, placebo-controlled, double-blind trial conducted in Asia in patients with Barcelona Clinic Liver Cancer (BCLC) Stage B or C HCC, who were previously treated with sorafenib or oxaliplatin-based chemotherapy and who were not amenable to or were refractory to local-regional therapy. Patients were also required to have Child-Pugh A liver function.

Patients with hepatitis B had treated controlled disease (HBV viral load <2000 IU/mL or $<10^4$ copies/mL). Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Patients with hepatic encephalopathy, main branch portal venous invasion, clinically apparent ascites, or esophageal or gastric variceal bleeding within the last 6 months were also ineligible.

Randomization was stratified by prior treatment: sorafenib vs. oxaliplatin-based chemotherapy, macrovascular invasion, and etiology (active HBV vs. others (active HCV, non-infected)). Patients were randomized (2:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or placebo.

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks. The main efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study enrolled 453 patients, and 360 (79%) had active hepatitis B. The population characteristics in patients with active hepatitis B were: median age of 52 years (range: 23 to 82), 16% age 65 or older; 86% male; 100% Asian; 42% ECOG PS of 0 and 58% ECOG PS of 1; 90% received prior sorafenib and 10% received prior oxaliplatin-based chemotherapy. Patient characteristics also included extrahepatic disease (77%), macrovascular invasion (10%), BCLC stage C (93%) and B (7%), and baseline AFP ≥200 ng/mL (57%).

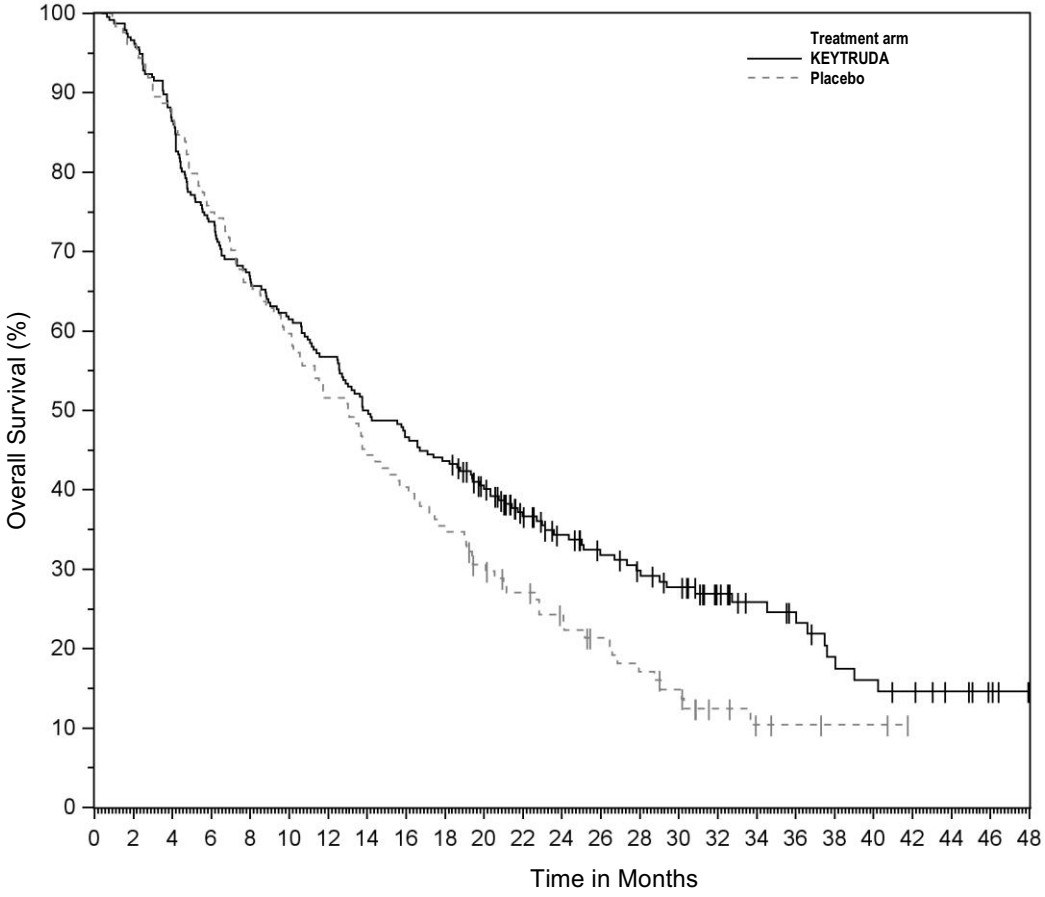
KEYNOTE-394 demonstrated improved OS in patients with HCC secondary to hepatitis B randomized to KEYTRUDA compared with placebo. Efficacy results are summarized in Table 89 and Figure 25.

Table 89: Efficacy Results in Patients with Hepatocellular Carcinoma in KEYNOTE-394

Endpoint	KEYTRUDA 200 mg every 3 weeks n=236	Placebo n=124
OS*		
Number (%) of patients with events	172 (73)	105 (85)
Median in months (95% CI)	13.9 (12.5, 17.9)	13.0 (10.1, 15.6)
Hazard ratio† (95% CI)	0.78 (0.61, 0.99)	
PFS‡		
Number (%) of patients with events	189 (80)	108 (87)
Median in months (95% CI)	2 (1.4, 2.7)	2.3 (1.4, 2.8)
Hazard ratio† (95% CI)	0.78 (0.61, 1.00)	
Objective Response Rate‡		
ORR§ (95% CI)	11% (7, 16)	1.6% (0.2, 5.7)
Number (%) of complete responses	2 (0.9%)	1 (0.8%)
Number (%) of partial responses	24 (10%)	1 (0.8%)
Duration of Response*	n=28	n=2
Median in months¶ (range)	23.9 (2.6+, 44.4+)	5.6 (3.0+, 5.6)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ Results at pre-specified interim OS analysis
§ Confirmed complete response or partial response
¶ Based on Kaplan-Meier estimate
\+ Denotes ongoing response

Figure 25: Kaplan-Meier Curve for Overall Survival in KEYNOTE-394



14.13 Biliary Tract Cancer

The efficacy of KEYTRUDA in combination with gemcitabine and cisplatin chemotherapy was investigated in KEYNOTE-966 (NCT04003636), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by region (Asia vs. non-Asia), locally advanced versus metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomized (1:1) to KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks, or placebo on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks. Study medications were administered via intravenous infusion. Treatment continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months. For gemcitabine, treatment could be continued beyond 8 cycles while for cisplatin, treatment could be administered for a maximum of 8 cycles.

Administration of KEYTRUDA with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumor status was performed at baseline and then every 6 weeks through 54 weeks, followed by every 12 weeks thereafter.

Study population characteristics were median age of 64 years (range: 23 to 85), 47% age 65 or older; 52% male; 49% White, 46% Asian, 1.3% Black or African American; 10% Hispanic or Latino; 46% ECOG PS of 0 and 54% ECOG PS of 1; 31% of patients had a history of hepatitis B infection, and 3% had a history of hepatitis C infection.

The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

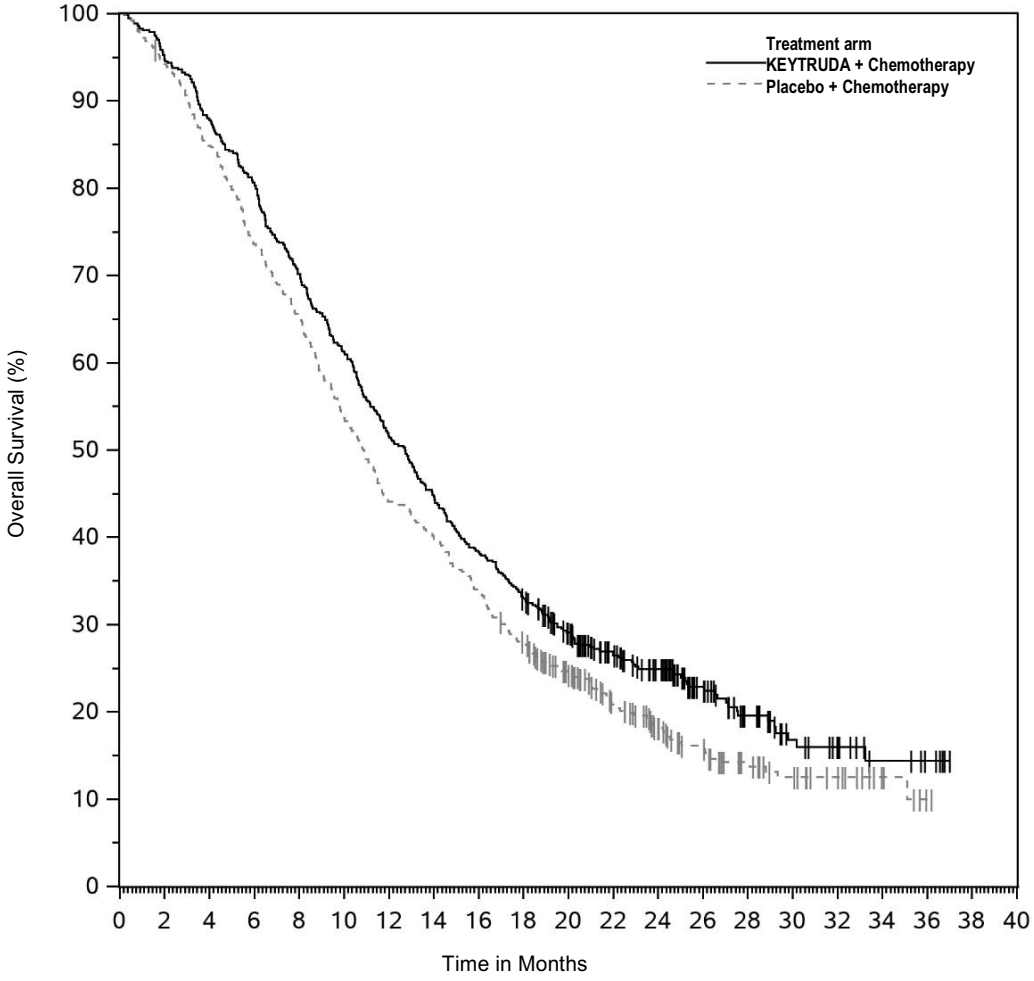
Table 90 and Figure 26 summarize the efficacy results for KEYNOTE-966.

Table 90: Efficacy Results in KEYNOTE-966

Endpoint	**KEYTRUDA 200 mg every 3 weeks with gemcitabine/cisplatin n=533**	**Placebo with gemcitabine/cisplatin n=536**
OS*		
Number of patients with event (%)	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio† (95% CI)	0.83 (0.72, 0.95)	
p-Value‡	0.0034	
PFS§		
Number (%) of patients with event	361 (68%)	391 (73%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (5.1, 6.6)
Hazard ratio† (95% CI)	0.86 (0.75, 1.00)	
p-Value‡	NS	
Objective Response Rate§		
ORR¶ (95% CI)	29% (25, 33)	29% (25, 33)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (27%)	146 (27%)
p-Value #	NS	
Duration of Response*	n=156	n=152
Median in months Þ (95% CI)	8.3 (6.9, 10.2)	6.8 (5.7, 7.1)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on a stratified log-rank test
§ Results at pre-specified final analysis of PFS and ORR
¶ Confirmed complete response or partial response
# One-sided p-Value based on the stratified Miettinen and Nurminen analysis
Þ Based on Kaplan-Meier estimate
NS = not significant

Figure 26: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966



Number at Risk																				
KEYTRUDA + Chemotherapy	533	505	469	430	374	326	275	238	204	175	142	108	88	56	35	21	16	8	5	0	0
Placebo + Chemotherapy	536	504	454	394	349	287	236	213	181	148	115	81	59	43	28	20	14	7	1	0	0

14.14 Merkel Cell Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-017 (NCT02267603) and KEYNOTE-913 (NCT03783078), two multicenter, non-randomized, open-label trials that enrolled 105 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 2 mg/kg (KEYNOTE-017) or 200 mg (KEYNOTE-913) every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months.

The major efficacy outcome measures were ORR and DoR as assessed by BICR per RECIST v1.1.

Among the 105 patients enrolled, the median age was 73 years (range: 38 to 91), 79% were age 65 or older; 62% were male; 80% were White, race in 19% was unknown or missing, and 1% were Asian; 53% had ECOG PS of 0, and 47% had ECOG PS of 1. Thirteen percent had stage IIIB disease and 84% had stage IV. Seventy-six percent of patients had prior surgery and 51% had prior radiation therapy.

Efficacy results are summarized in Table 91.

Table 91: Efficacy Results in KEYNOTE-017 and KEYNOTE-913

Endpoint	KEYNOTE-017 KEYTRUDA 2 mg/kg every 3 weeks n=50	KEYNOTE-913 KEYTRUDA 200 mg or 2 mg/kg every 3 weeks n=55
Objective Response Rate		
ORR (95% CI)	56% (41, 70)	49% (35, 63)
Complete responses, n (%)	12 (24%)	9 (16%)
Partial responses, n (%)	16 (32%)	18 (33%)
Duration of Response	**n=28**	**n=27**
Median DoR in months (range)	NR (5.9, 34.5+)	NR (4.8, 25.4+)
Patients with duration ≥6 months, n (%)	27 (96%)	25 (93%)
Patients with duration ≥12 months, n (%)	15 (54%)	19 (70%)

\+ Denotes ongoing response
NR = not reached

14.15 Renal Cell Carcinoma

First-line treatment with axitinib

KEYNOTE-426

The efficacy of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease requiring systemic immunosuppression within the last 2 years were ineligible. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”).

Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive cycles (6 weeks) could increase to 7 mg and then subsequently to 10 mg twice daily. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

Treatment with KEYTRUDA and axitinib continued until RECIST v1.1-defined progression of disease or unacceptable toxicity. Administration of KEYTRUDA and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter.

The study population characteristics were: median age of 62 years (range: 26 to 90), 38% age 65 or older; 73% male; 79% White and 16% Asian; 20% and 80% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; and patient distribution by IMDC risk categories was 31% favorable, 56% intermediate, and 13% poor.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the first pre-specified interim analysis in patients randomized to KEYTRUDA in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. An updated OS analysis was conducted when 418 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 92 and Figure 27 summarize the efficacy results for KEYNOTE-426.

Table 92: Efficacy Results in KEYNOTE-426

Endpoint	KEYTRUDA 200 mg every 3 weeks and Axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	<0.0001‡	
Updated OS		
Number of patients with event (%)	193 (45%)	225 (52%)
Median in months (95% CI)	45.7 (43.6, NR)	40.1 (34.3, 44.2)
Hazard ratio* (95% CI)	0.73 (0.60, 0.88)	
PFS		
Number of patients with event (%)	183 (42%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.0 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value†	0.0001§	
Objective Response Rate		
ORR¶ (95% CI)	59% (54, 64)	36% (31, 40)
Complete response rate	6%	2%
Partial response rate	53%	34%
p-Value#	<0.0001	

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).

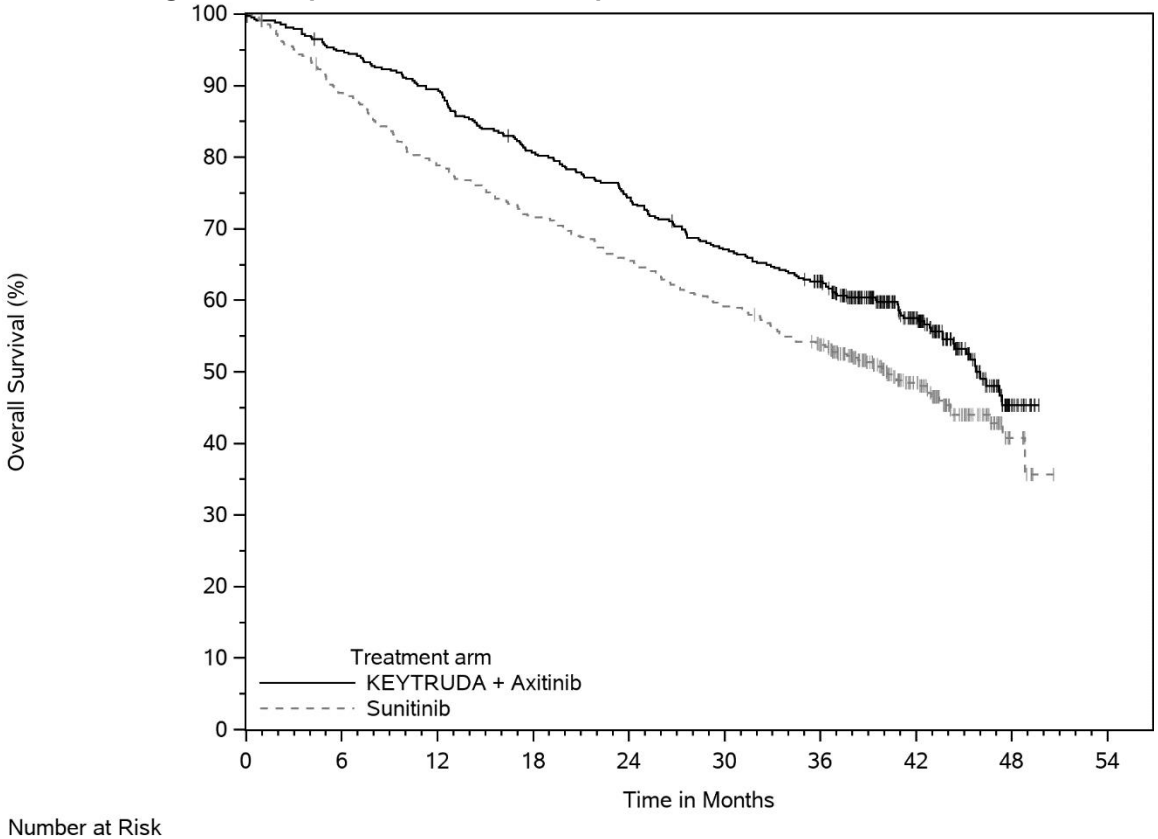
§ p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).

¶ Response: Best objective response as confirmed complete response or partial response

Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

NR = not reached

Figure 27: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-426



Number at Risk

KEYTRUDA + Axitinib	432	407	384	345	318	286	259	141	16	0
Sunitinib	429	379	336	306	279	252	224	110	12	0

In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR of 1.17 (95% CI: 0.76, 1.80), 0.67 (95% CI: 0.52, 0.86), 0.64 (95% CI: 0.52, 0.80), and 0.51 (95% CI: 0.32, 0.81), respectively.

First-line treatment with lenvatinib

KEYNOTE-581

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581 (NCT02811861), a multicenter, open-label, randomized trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America versus Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable versus intermediate versus poor risk).

Patients were randomized (1:1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.
- Lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a

maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 8 weeks.

The study population characteristics were: median age of 62 years (range: 29 to 88 years), 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by MSKCC risk categories was 27% favorable, 64% intermediate, and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

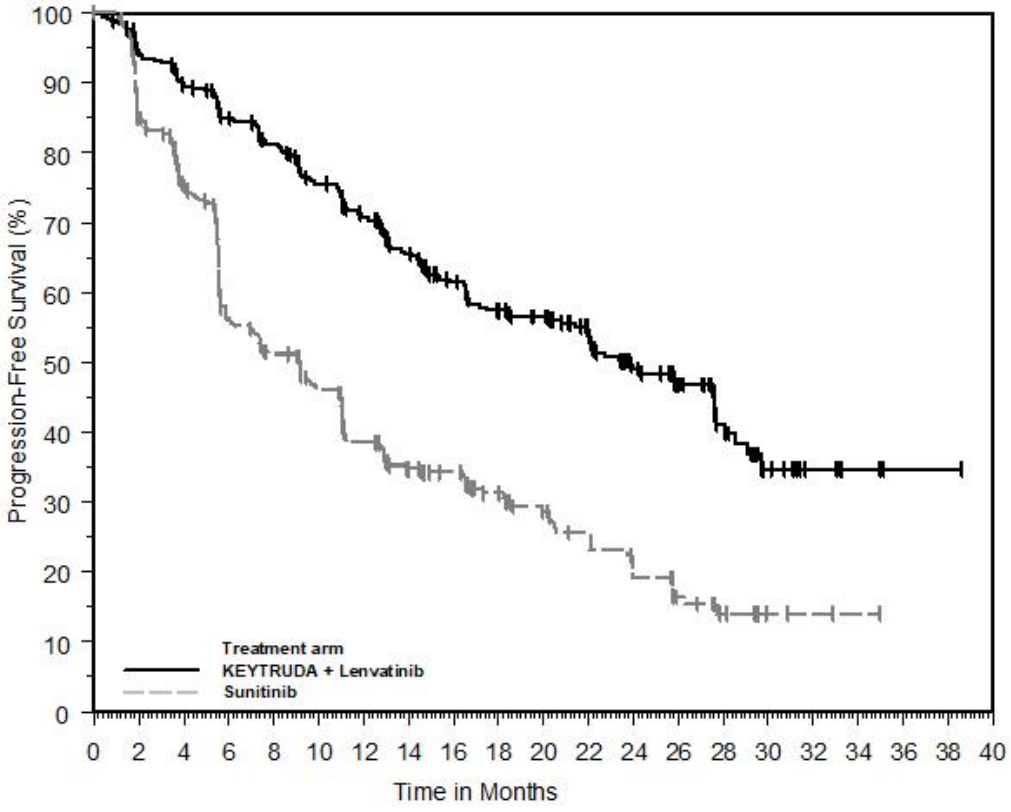
The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to RECIST v1.1, and OS. Additional efficacy outcome measures included confirmed ORR as assessed by IRC. KEYTRUDA in combination with lenvatinib demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. An updated OS analysis was conducted when 304 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 93 and Figures 28 and 29 summarize the efficacy results for KEYNOTE-581.

Table 93: Efficacy Results in KEYNOTE-581

Endpoint	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=355	Sunitinib n=357
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45%)	205 (57%)
Progressive disease	145 (41%)	196 (55%)
Death	15 (4%)	9 (3%)
Median PFS in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value†	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (23%)	101 (28%)
Median OS in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.88)	
p-Value†	0.0049	
Updated OS		
Number of deaths, n (%)	149 (42%)	159 (45%)
Median OS in months (95% CI)	53.7 (48.7, NR)	54.3 (40.9, NR)
Hazard ratio* (95% CI)	0.79 (0.63, 0.99)	
Objective Response Rate (Confirmed)		
ORR, n (%)	252 (71%)	129 (36%)
(95% CI)	(66, 76)	(31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value‡	<0.0001	

Tumor assessments were based on RECIST 1.1; only confirmed responses are included for ORR.
Data cutoff date = 28 Aug 2020, Updated OS cutoff date = 31 July 2022
CI = confidence interval; NR= Not reached
* Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
† Two-sided p-Value based on stratified log-rank test.
‡ Two-sided p-Value based upon CMH test.

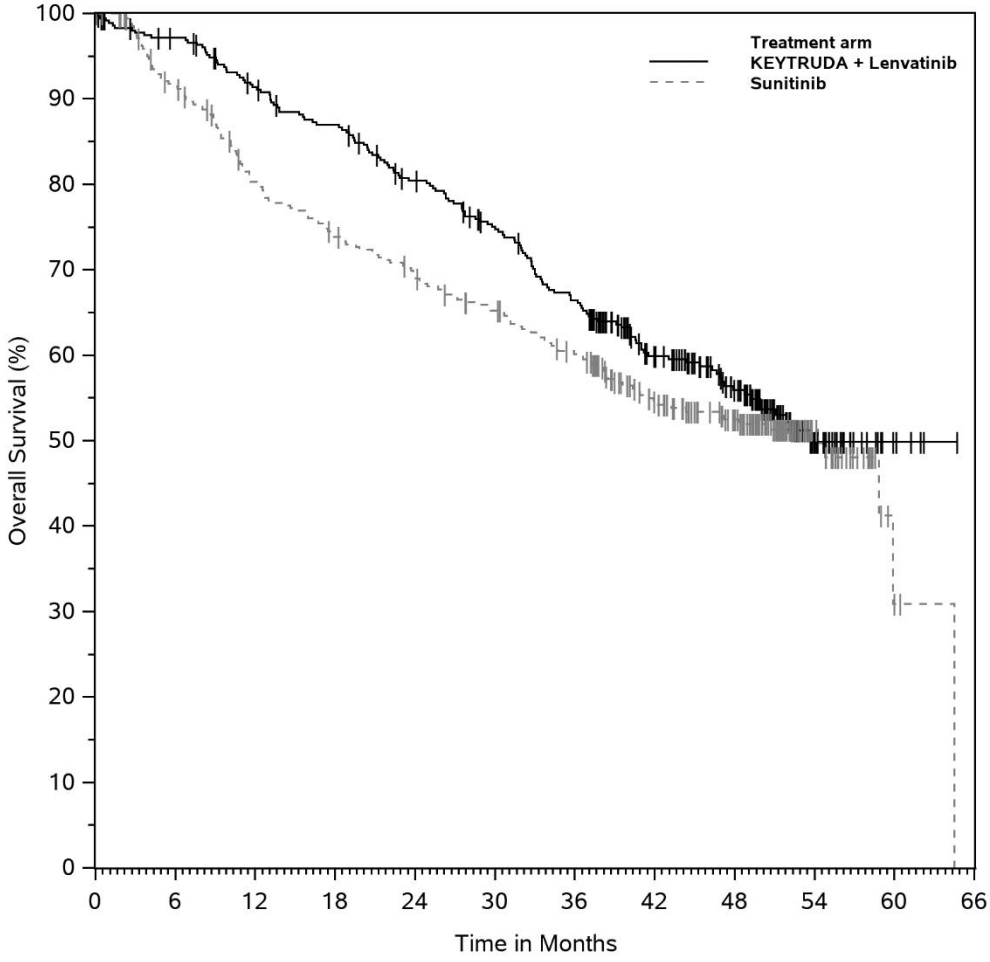
Figure 28: Kaplan-Meier Curve for PFS in KEYNOTE-581



Number at Risk

KEYTRUDA + Lenvatinib:	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Sunitinib:	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0	0	0

Figure 29: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-581



Number at Risk

KEYTRUDA + Lenvatinib	355	338	313	296	269	245	216	158	117	34	5	0
Sunitinib	357	308	264	242	226	208	188	145	108	33	3	0

KEYNOTE-B61

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-B61 (NCT04704219), a multicenter, single-arm trial that enrolled 160 patients with advanced/metastatic non-clear cell RCC in the first-line setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 400 mg every 6 weeks in combination with lenvatinib 20 mg orally once daily. KEYTRUDA was continued for a maximum of 24 months; however, lenvatinib could be continued beyond 24 months. Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years); 71% male; 86% White, 8% Asian, and 3% Black; <1% Hispanic or Latino; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, <1% medullary, 13% unclassified, and 6% other; patient distribution by IMDC risk categories was 35% favorable, 54% intermediate, and 10% poor. Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The major efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Additional efficacy outcome measures included DOR as assessed by BICR using RECIST 1.1. Efficacy results are summarized in Table 94.

Table 94: Efficacy Results in KEYNOTE-B61

Endpoint	KEYTRUDA 400 mg every 6 weeks and Lenvatinib n=158
Objective Response Rate (Confirmed)	
ORR (95% CI)	51% (43, 59)
Complete response	8%
Partial response	42%
Duration of Response*	
Median in months (range)	19.5 (1.5+, 23.5+)

CI = confidence interval
* Based on Kaplan-Meier estimates
\+ Denotes ongoing response

Adjuvant Treatment of RCC (KEYNOTE-564)

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564 (NCT03142334), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening. Patients were excluded from the trial if they had received prior systemic therapy for advanced RCC. Patients with active autoimmune disease or a medical condition that required immunosuppression were also ineligible. Patients were randomized to KEYTRUDA 200 mg administered intravenously every 3 weeks or placebo for up to 1 year until disease recurrence or unacceptable toxicity. Randomization was stratified by metastasis status (M0, M1 NED); M0 group was further stratified by ECOG PS (0,1) and geographic region (US, non-US).

The study population characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; 75% White, 14% Asian, 9% Unknown, 1% Black or African American, 1% American Indian or Alaska Native, 1% Multiracial; 13% Hispanic or Latino, 78% Not Hispanic or Latino, 8% Unknown; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent of patients enrolled had N0 disease; 11% had sarcomatoid features; 86% were intermediate-high risk; 8% were high risk; and 6% were M1 NED. Ninety-two percent of patients had a radical nephrectomy, and 8% had a partial nephrectomy.

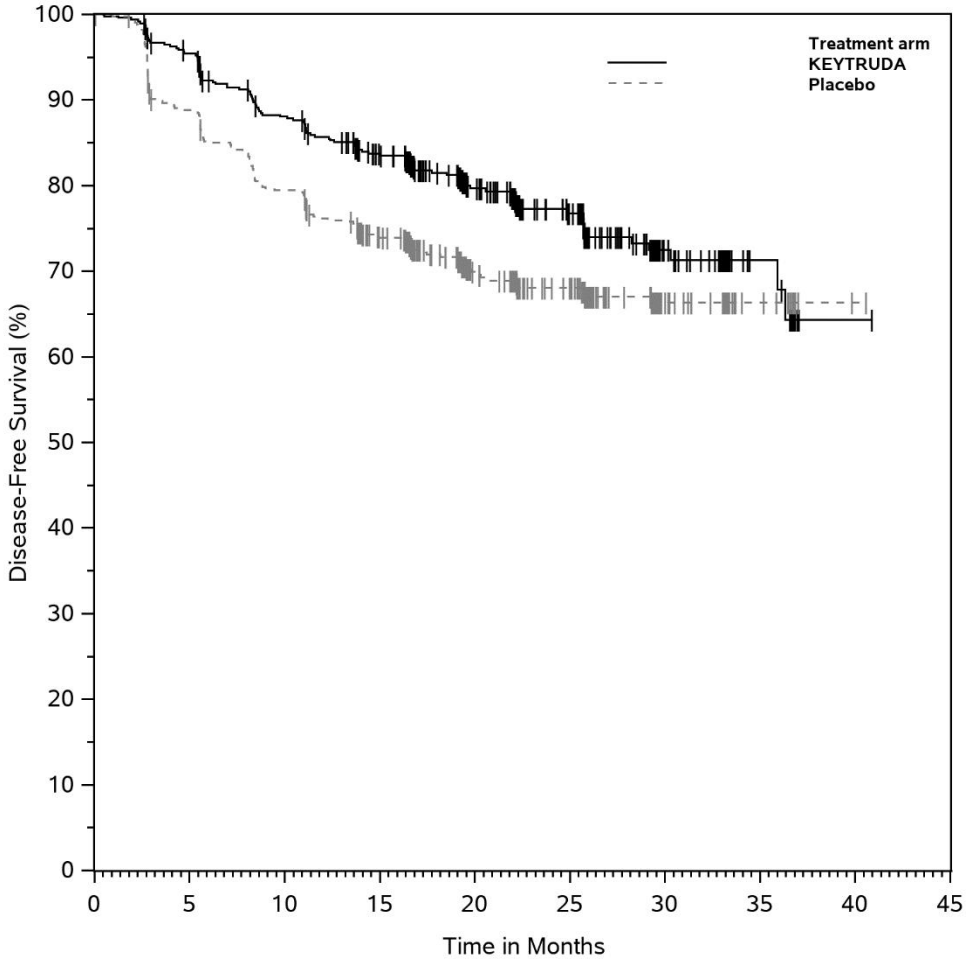
The major efficacy outcome measure was investigator-assessed disease-free survival (DFS), defined as time to recurrence, metastasis, or death. An additional outcome measure was OS. A statistically significant improvement in DFS was demonstrated at the pre-specified interim analysis in patients randomized to the KEYTRUDA arm compared with placebo. At the time of the DFS analysis, OS data were not mature, with 5% deaths in the overall population. Efficacy results are summarized in Table 95 and Figure 30.

Table 95: Efficacy Results in KEYNOTE-564

Endpoint	KEYTRUDA 200 mg every 3 weeks n=496	Placebo n=498
DFS		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.68 (0.53, 0.87)	
p-Value†	0.0010±	
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
± p-Value (one-sided) is compared with a boundary of 0.0114.
NR = not reached

Figure 30: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-564



Number at Risk

KEYTRUDA	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

14.16 Endometrial Carcinoma

In Combination with Paclitaxel and Carboplatin for the Treatment of Primary Advanced or Recurrent Endometrial Carcinoma

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868/NRG-GY018 (NCT03914612), a multicenter, randomized, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma. The study design included two separate cohorts based on MMR status; 222 (27%) patients were in dMMR cohort, 588 (73%) patients were in pMMR cohort. The trial enrolled measurable Stage III, measurable Stage IVA, Stage IVB or recurrent endometrial cancer (with or without measurable disease). Patients who had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting were eligible. Patients who had received prior adjuvant chemotherapy were only eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy.

Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

All study medications were administered as an intravenous infusion on Day 1 of each treatment cycle. Treatment continued until disease progression, unacceptable toxicity, or a maximum of 20 cycles (up to approximately 24 months). Patients with measurable disease who had RECIST-defined stable disease or partial response at the completion of cycle 6 were permitted to continue receiving paclitaxel and carboplatin with KEYTRUDA or placebo for up to 10 cycles as determined by the investigator. Assessment of tumor status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter. The major efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. An additional efficacy outcome measure was OS.

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55% age 65 or older; 79% White, 9% Black, and 3% Asian; 5% Hispanic or Latino; 64% ECOG PS of 0, 33% ECOG PS of 1, and 3% ECOG PS of 2; 61% had recurrent disease and 39% had primary or persistent disease; 5% received prior adjuvant chemotherapy and 43% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (81%), adenocarcinoma NOS (11%), serous carcinoma (2%), and other (6%).

The pMMR population characteristics were: median age of 66 years (range: 29 to 94), 54% age 65 or older; 72% White, 16% Black, and 5% Asian; 6% Hispanic or Latino; 67% ECOG PS of 0, 30% ECOG PS of 1, and 3% ECOG PS of 2; 56% had recurrent disease and 44% had primary or persistent disease; 26% received prior adjuvant chemotherapy and 41% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (52%), serous carcinoma (26%), adenocarcinoma NOS (10%), clear cell carcinoma (7%), and other (5%).

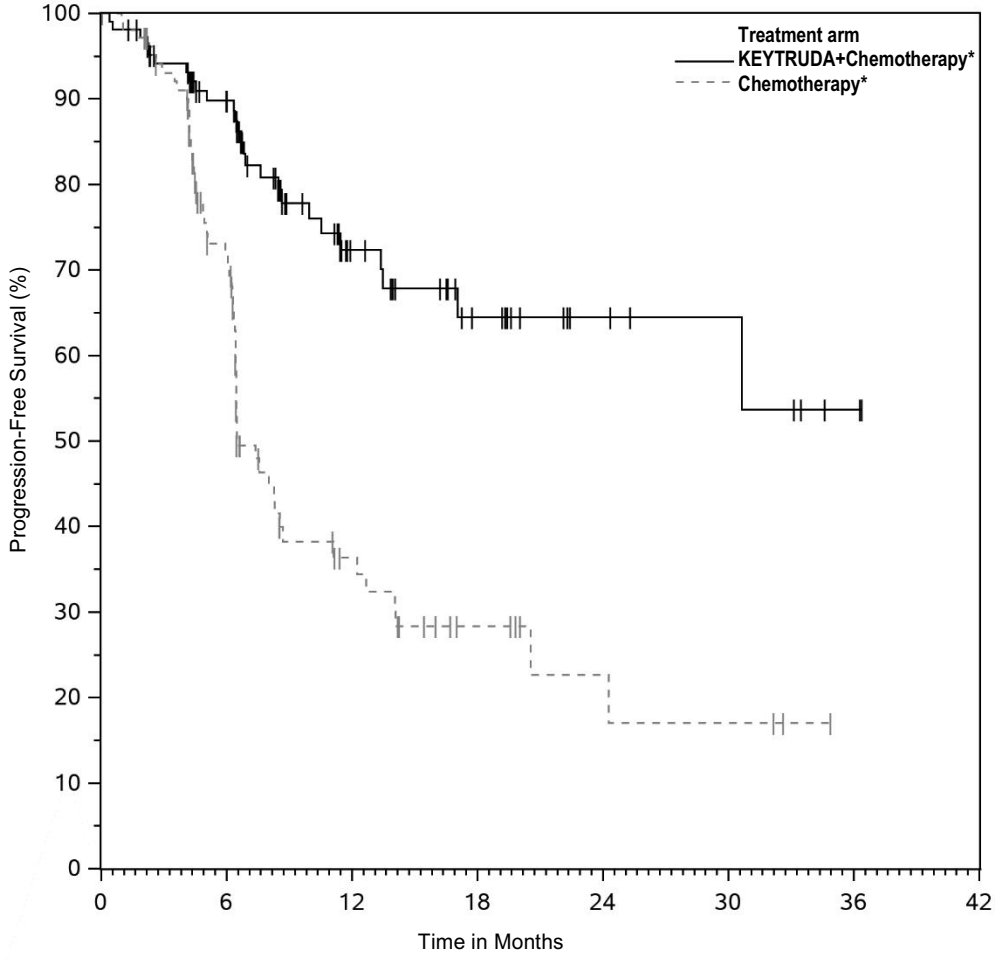
The trial demonstrated statistically significant improvements in PFS for patients randomized to KEYTRUDA in combination with paclitaxel and carboplatin compared to placebo in combination with paclitaxel and carboplatin in both the dMMR and pMMR populations. Table 96 and Figures 31 and 32 summarize the efficacy results for KEYNOTE-868 by MMR status. At the time of the PFS analysis, OS data were not mature with 12% deaths in the dMMR population and 17% deaths in the pMMR population.

Table 96: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	KEYTRUDA with paclitaxel and carboplatin n=110	Placebo with paclitaxel and carboplatin n=112	KEYTRUDA with paclitaxel and carboplatin n=294	Placebo with paclitaxel and carboplatin n=294
PFS*				
Number (%) of patients with event	26 (24%)	57 (51%)	91 (31%)	124 (42%)
Median in months (95% CI)	NR (30.7, NR)	6.5 (6.4, 8.7)	11.1 (8.7, 13.5)	8.5 (7.2, 8.8)
Hazard ratio† (95% CI)	0.30 (0.19, 0.48)		0.60 (0.46, 0.78)	
p-Value‡	<0.0001		<0.0001	

* Based on interim PFS analysis; the information fractions for interim analyses were 49% for dMMR and 55% for pMMR.
† Based on the stratified Cox proportional hazard model
‡ Based on the stratified log-rank test
NR = not reached

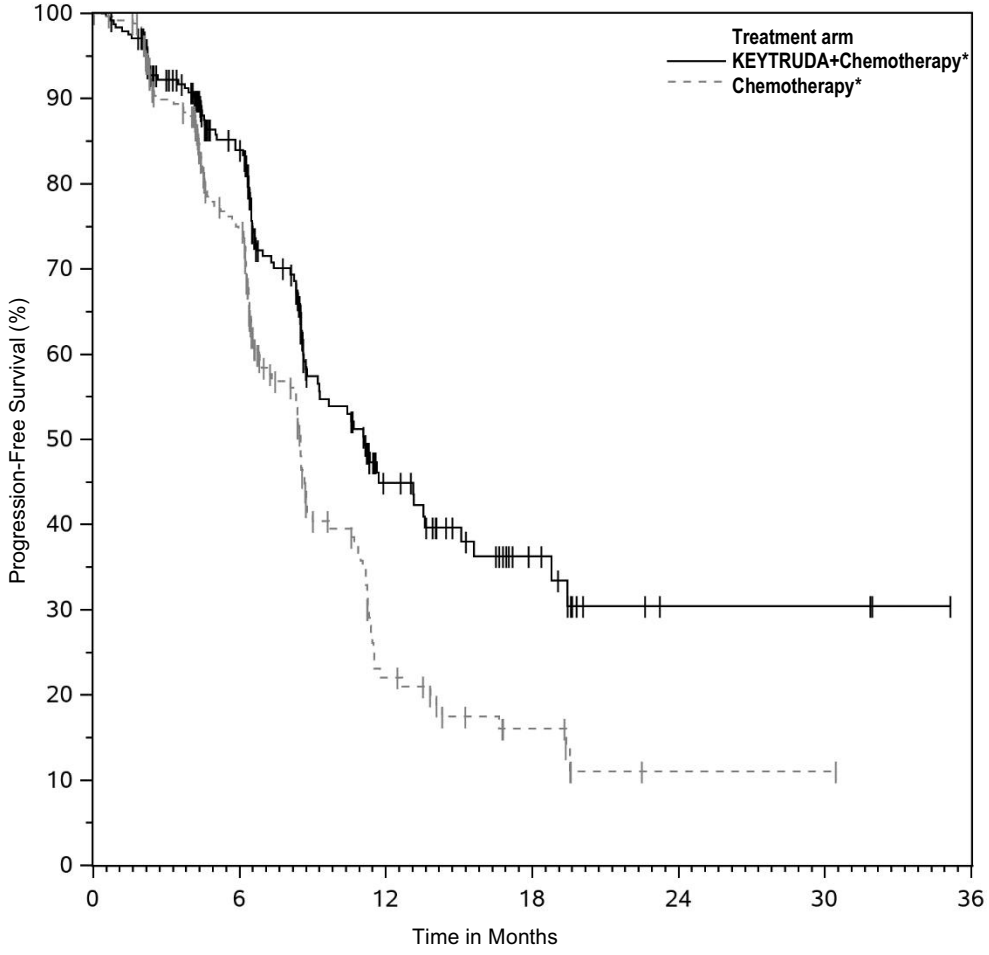
Figure 31: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



Number at Risk								
KEYTRUDA+Chemotherapy*	110	78	33	17	8	6	2	0
Chemotherapy*	112	58	18	8	4	3	0	0

*Chemotherapy (paclitaxel and carboplatin)

Figure 32: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



Number at Risk							
KEYTRUDA+Chemotherapy*	294	140	36	14	3	3	0
Chemotherapy*	294	126	22	8	1	1	0

*Chemotherapy (paclitaxel and carboplatin)

In Combination with Lenvatinib for the Treatment of Advanced Endometrial Carcinoma That Is pMMR or Not MSI-H

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775 (NCT03517449), a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients with endometrial carcinoma that were pMMR (using the VENTANA MMR RxDx Panel test) or not MSI-H were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- Investigator's choice, consisting of either doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 given weekly, 3 weeks on/1 week off.

Treatment with KEYTRUDA and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR and DoR, as assessed by BICR.

Among the 697 pMMR patients, 346 patients were randomized to KEYTRUDA in combination with lenvatinib, and 351 patients were randomized to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The pMMR population characteristics were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

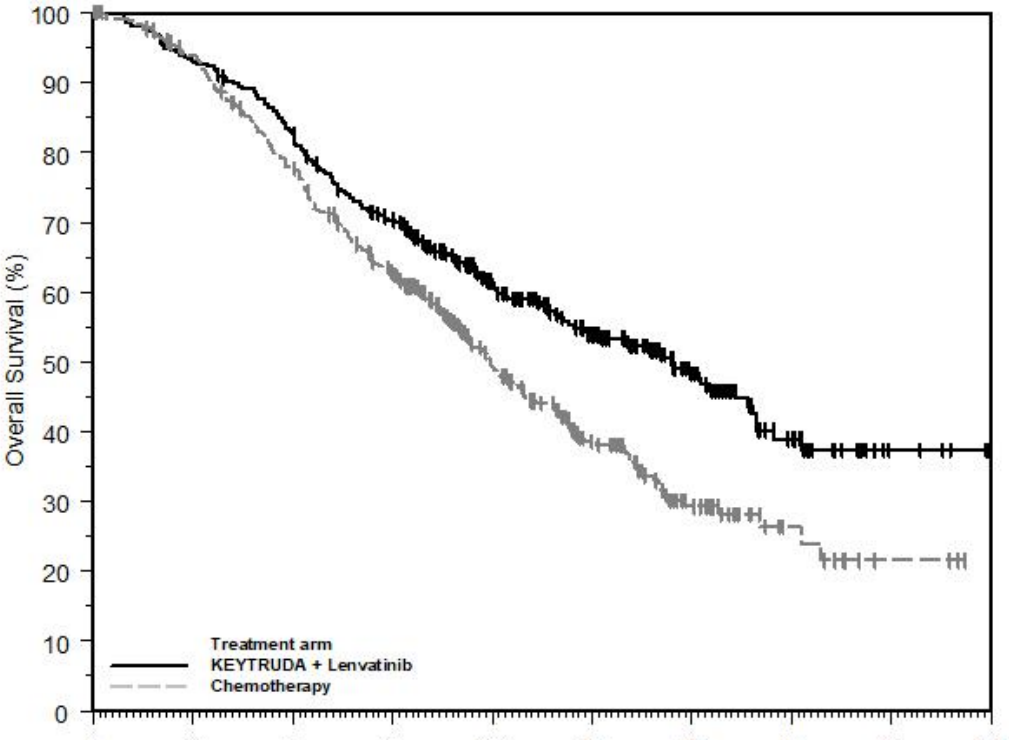
Efficacy results for the pMMR or not MSI-H patients are summarized in Table 97 and Figures 33 and 34.

Table 97: Efficacy Results in KEYNOTE-775

	Endometrial Carcinoma (pMMR or not MSI-H)	
Endpoint	**KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=346**	**Doxorubicin or Paclitaxel n=351**
OS		
Number (%) of patients with event	165 (48%)	203 (58%)
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
Hazard ratio* (95% CI)	0.68 (0.56, 0.84)	
p-Value†	0.0001	
PFS		
Number (%) of patients with event	247 (71%)	238 (68%)
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
Hazard ratio* (95% CI)	0.60 (0.50, 0.72)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	30% (26, 36)	15% (12, 19)
Complete response rate	5%	3%
Partial response rate	25%	13%
p-Value§	<0.0001	
Duration of Response	n=105	n=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

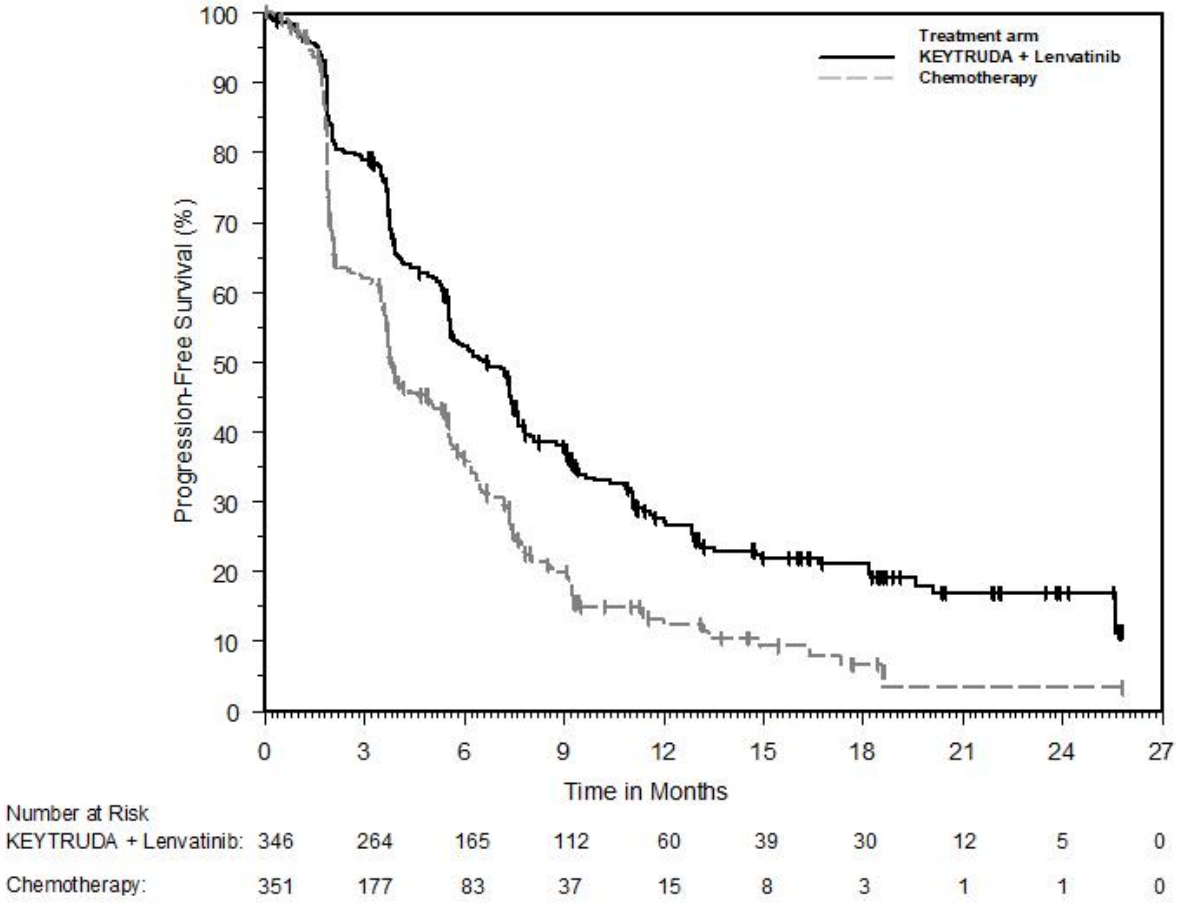
* Based on the stratified Cox regression model
† Based on stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation

Figure 33: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775 (pMMR or Not MSI-H)



Number at Risk										
KEYTRUDA + Lenvatinib:	346	322	285	232	160	109	62	28	5	0
Chemotherapy:	351	319	262	201	120	70	33	11	3	0

Figure 34: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775 (pMMR or Not MSI-H)



As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 90 patients evaluated, the baseline characteristics were: median age of 64 years (range: 42 to 86); 83% White, 8% Asian, and 3% Black; 12% Hispanic or Latino; 39% ECOG PS of 0 and 61% ECOG PS of 1; 96% had M1 disease and 4% had M0 disease at study entry; and 51% had one and 48% had two or more prior lines of therapy. Nine patients received only adjuvant therapy and one patient received only neoadjuvant and adjuvant therapy before participating in the study.

Efficacy results are summarized in Table 98.

Table 98: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158

Endpoint	KEYTRUDA n=90*
Objective Response Rate	
ORR (95% CI)	46% (35, 56)
Complete response rate	12%
Partial response rate	33%
Duration of Response	n=41
Median in months (range)	NR (2.9, 55.7+)
% with duration ≥12 months	68%
% with duration ≥24 months	44%

* Median follow-up time of 16.0 months (range 0.5 to 62.1 months)
\+ Denotes ongoing response
NR = not reached

14.17 Tumor Mutational Burden-High Cancer

The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with high tumor mutation burden (TMB-H) who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). The trial excluded patients who previously received an anti-PD-1 or other immune-modulating monoclonal antibody, or who had an autoimmune disease, or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Assessment of tumor status was performed every 9 weeks for the first 12 months and every 12 weeks thereafter.

The statistical analysis plan pre-specified ≥10 and ≥13 mutations per megabase using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The major efficacy outcome measures were ORR and DoR in patients who received at least one dose of KEYTRUDA as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

In KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ≥10 mutations per megabase. Among the 102 patients with TMB-H advanced solid tumors, the study population characteristics were: median age of 61 years (range: 27 to 80), 34% age 65 or older; 34% male; 81% White; and 41% ECOG PS of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

Efficacy results are summarized in Tables 99 and 100.

Table 99: Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158

Endpoint	KEYTRUDA 200 mg every 3 weeks	
	TMB ≥10 mut/Mb n=102*	TMB ≥13 mut/Mb n=70
Objective Response Rate		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
Duration of Response	n=30	n=26
Median in months (range)†	NR (2.2+, 34.8+)	NR (2.2+, 34.8+)
% with duration ≥12 months	57%	58%
% with duration ≥24 months	50%	50%

* Median follow-up time of 11.1 months
† From product-limit (Kaplan-Meier) method for censored data
\+ Denotes ongoing response
NR = not reached

Table 100: Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	18.8+
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		(8.2, 33.2+)
Mesothelioma cancer	1	PD		

* No TMB-H patients were identified in the cholangiocarcinoma cohort
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

In an exploratory analysis in 32 patients enrolled in KEYNOTE-158 whose cancer had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI: 4%, 29%), including two complete responses and two partial responses.

14.18 Cutaneous Squamous Cell Carcinoma

The efficacy of KEYTRUDA was investigated in patients with recurrent or metastatic cSCC or locally advanced cSCC enrolled in KEYNOTE-629 (NCT03284424), a multicenter, multi-cohort, non-randomized, open-label trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until documented disease progression, unacceptable toxicity, or a maximum of 24 months. Patients with initial radiographic disease progression could receive additional doses of KEYTRUDA during confirmation of progression unless disease progression was symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumor status was performed every 6 weeks during the first year, and every 9 weeks during the second year. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 105 patients with recurrent or metastatic cSCC treated, the study population characteristics were: median age of 72 years (range: 29 to 95), 71% age 65 or older; 76% male; 71% White, 25% race

unknown; 34% ECOG PS of 0 and 66% ECOG PS of 1. Forty-five percent of patients had locally recurrent only cSCC, 24% had metastatic only cSCC, and 31% had both locally recurrent and metastatic cSCC. Eighty-seven percent received one or more prior lines of therapy; 74% received prior radiation therapy.

Among the 54 patients with locally advanced cSCC treated, the study population characteristics were: median age of 76 years (range: 35 to 95), 80% age 65 or older; 72% male; 83% White, 13% race unknown; 41% ECOG PS of 0 and 59% ECOG PS of 1. Twenty-two percent received one or more prior lines of therapy; 63% received prior radiation therapy.

Efficacy results are summarized in Table 101.

Table 101: Efficacy Results in KEYNOTE-629

Endpoint	KEYTRUDA Recurrent or Metastatic cSCC n=105	KEYTRUDA Locally Advanced cSCC n=54
Objective Response Rate		
ORR (95% CI)	35% (26, 45)	50% (36, 64)
Complete response rate	11%	17%
Partial response rate	25%	33%
Duration of Response*	n=37	n=27
Median in months (range)	NR (2.7, 30.4+)	NR (1.0+, 17.2+)
% with duration ≥6 months	76%	81%
% with duration ≥12 months	68%	37%

* Median follow-up time: recurrent or metastatic cSCC: 23.8 months; locally advanced cSCC: 13.4 months

\+ Denotes ongoing response

14.19 Triple-Negative Breast Cancer

Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The efficacy of KEYTRUDA in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522 (NCT03036488), a randomized (2:1), multicenter, double-blind, placebo-controlled trial conducted in 1174 patients with newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement). Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

Patients were randomized (2:1) to one of the following two treatment arms; all study medications were administered intravenously:

- **Arm 1:**
  - Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

        -or-

      - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

        -and-
    - Paclitaxel 80 mg/m^2 every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

- Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
    - Doxorubicin 60 mg/m^2 ***-or-*** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen ***-and-***
    - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, nine cycles of KEYTRUDA 200 mg every 3 weeks were administered.

- **Arm 2:**
    - Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
        - Carboplatin
            - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

              -or-
            - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

              -and-
        - Paclitaxel 80 mg/m^2 every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
    - Followed by four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
        - Doxorubicin 60 mg/m^2 ***-or-*** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen ***-and-***
        - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
    - Following surgery, nine cycles of placebo every 3 weeks were administered.

The main efficacy outcomes were pCR rate and EFS. pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome was overall survival (OS).

The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 4.5% Black, and 1.8% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumor 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall Stage II and 25% were Stage III.

Table 102 and Figure 35 summarize the efficacy results for KEYNOTE-522. At the protocol pre-specified IA4 interim analysis of OS, OS data were not mature with 45% of the required events for the final analysis.

Table 102: Efficacy Results in KEYNOTE-522

Endpoint	KEYTRUDA 200 mg every 3 weeks with chemotherapy/KEYTRUDA n=784	Placebo with chemotherapy/Placebo n=390
pCR (ypT0/Tis ypN0)*		
Number of patients with pCR	494	217
pCR Rate (%), (95% CI)	63.0 (59.5, 66.4)	55.6 (50.6, 60.6)
Treatment difference (%) estimate (95% CI)[†,‡]	7.5 (1.6, 13.4)	
EFS		
Number of patients with event (%)	123 (16%)	93 (24%)
Hazard ratio (95% CI)[§]	0.63 (0.48, 0.82)	
p-Value[¶,#]	0.00031	

* Based on the entire intention-to-treat population n=1174 patients

† Based on a pre-specified pCR interim analysis in n=602 patients, the pCR rate difference was statistically significant (p=0.00055 compared to a significance level of 0.003).

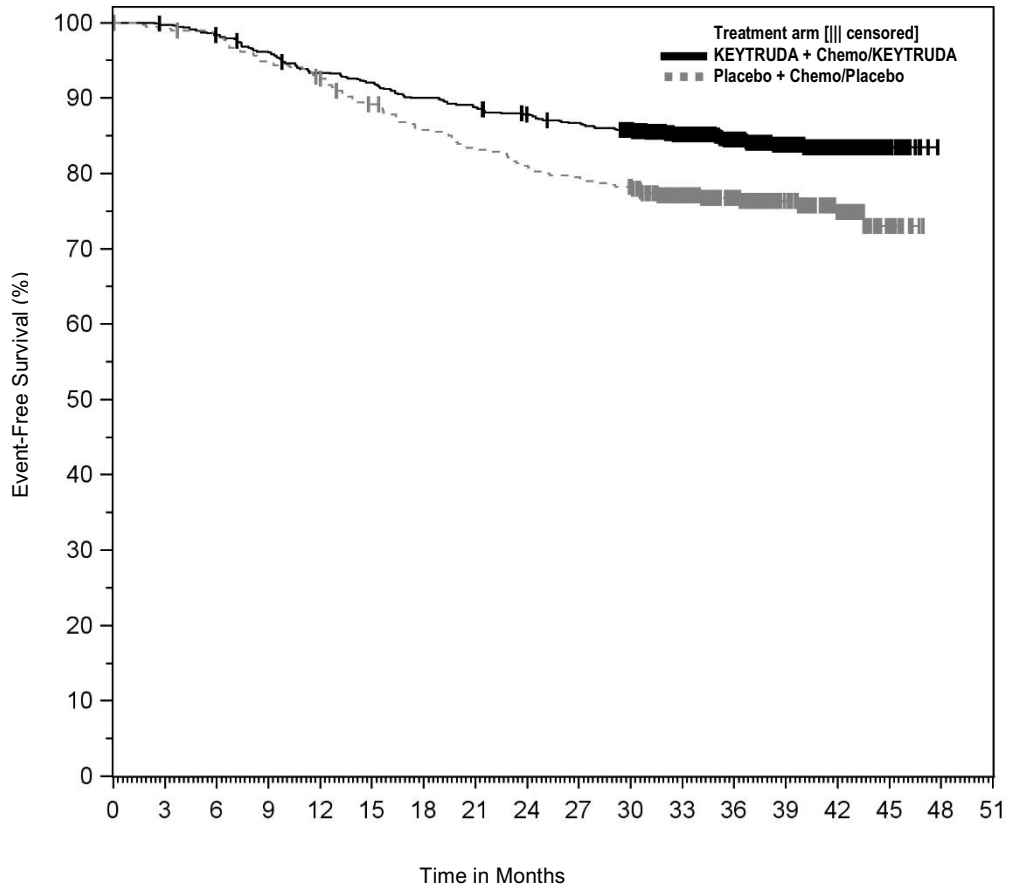
‡ Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin

§ Based on stratified Cox regression model

¶ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052)

Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin

Figure 35: Kaplan-Meier Curve for Event-Free Survival in KEYNOTE-522



Locally Recurrent Unresectable or Metastatic TNBC

The efficacy of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial conducted in 847 patients with locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, who had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by chemotherapy treatment (paclitaxel or paclitaxel protein-bound vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS ≥1 vs. CPS <1) according to the PD-L1 IHC 22C3 pharmDx kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

Patients were randomized (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

- Placebo on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, tested in the subgroup of patients with CPS ≥10. Additional efficacy outcome measures were ORR and DoR as assessed by BICR.

The study population characteristics for patients were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of patients had tumor PD-L1 expression CPS ≥1 and 38% had tumor PD-L1 expression CPS ≥10.

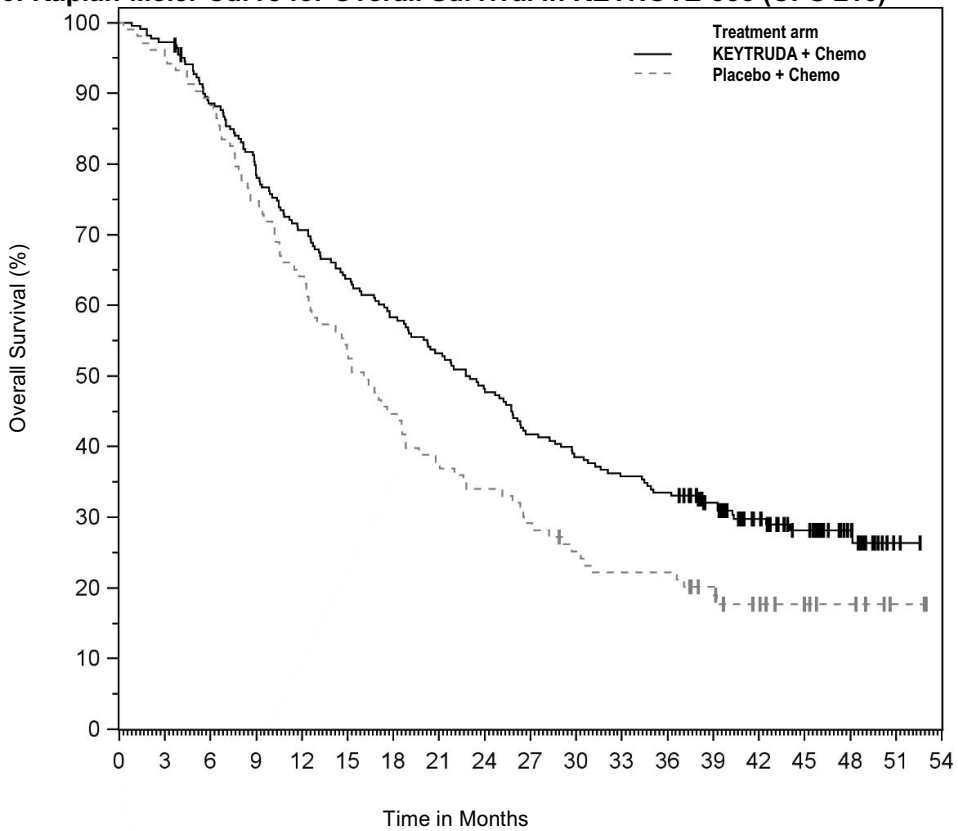
Table 103 and Figures 36 and 37 summarize the efficacy results for KEYNOTE-355.

Table 103: Efficacy Results in KEYNOTE-355 (CPS ≥10)

Endpoint	**KEYTRUDA 200 mg every 3 weeks with chemotherapy n=220**	**Placebo every 3 weeks with chemotherapy n=103**
OS*		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio† (95% CI)	0.73 (0.55, 0.95)	
p-Value‡	0.0093	
PFS§		
Number of patients with event (%)	136 (62%)	79 (77%)
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
Hazard ratio† (95% CI)	0.65 (0.49, 0.86)	
p-Value¶	0.0012	
Objective Response Rate (Confirmed)*		
ORR (95% CI)	53% (46, 59)	41% (31, 51)
Complete response rate	17%	14%
Partial response rate	35%	27%
Duration of Response*	**n=116**	**n=42**
Median in months (95% CI)	12.8 (9.9, 25.9)	7.3 (5.5, 15.4)

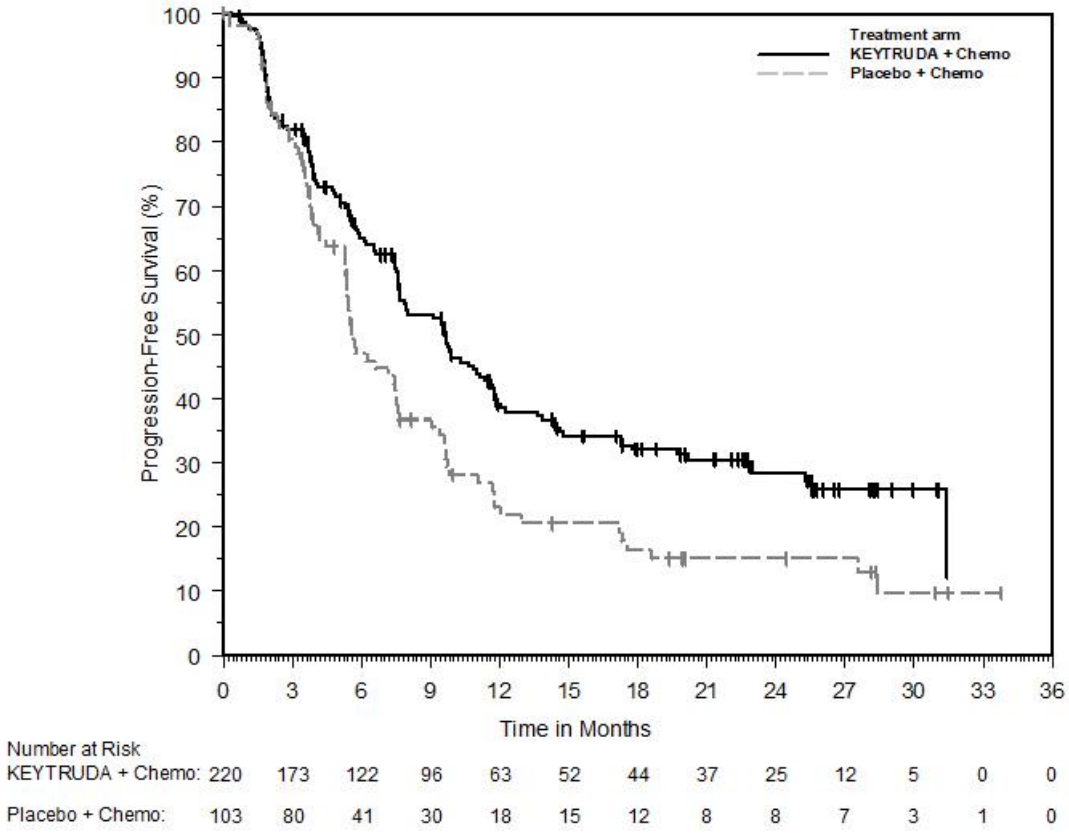
* Based on the pre-specified final analysis
† Based on stratified Cox regression model
‡ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.0113)
§ Based on a pre-specified interim analysis
¶ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.00411)

Figure 36: Kaplan-Meier Curve for Overall Survival in KEYNOTE-355 (CPS ≥10)



Number at Risk																		
KEYTRUDA + Chemo	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo + Chemo	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

Figure 37: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS ≥10)



14.20 Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks

The efficacy and safety of KEYTRUDA using a dosage of 400 mg every 6 weeks for the classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma indications for adults was primarily based on the dose/exposure efficacy and safety relationships and observed pharmacokinetic data in patients with melanoma *[see Clinical Pharmacology (12.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA injection (clear to slightly opalescent, colorless to slightly yellow solution):

Carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02)
Carton containing two 100 mg/4 mL (25 mg/mL), single-dose vials (NDC 0006-3026-04)
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.

- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, or Type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)]*.
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.1)]*.
- Other immune-mediated adverse reactions:
    - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions (5.1)]*.
    - Advise patients of the risk of solid organ transplant rejection and other transplant (including corneal graft) rejection. Advise patients to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection and other transplant (including corneal graft) rejection *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)].*

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].*
- Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.1)]*.

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 25 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 4 mL of concentrate contains 100 mg of pembrolizumab.
Each mL of concentrate contains 25 mg of pembrolizumab.

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection (see section 5.1).

Non-small cell lung carcinoma (NSCLC)

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1).

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (for selection criteria, see section 5.1).

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

Classical Hodgkin lymphoma (cHL)

KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see section 5.1).

Head and neck squamous cell carcinoma (HNSCC)

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy (see section 5.1).

Renal cell carcinoma (RCC)

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, see section 5.1).

Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers

Colorectal cancer (CRC)
KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- first-line treatment of metastatic colorectal cancer;
- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

Non-colorectal cancers
KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10 (see section 5.1).

Triple-negative breast cancer (TNBC)

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence (see section 5.1).

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease (see section 5.1).

Endometrial carcinoma (EC)

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Cervical cancer

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1).

Biliary tract carcinoma (BTC)

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

4.2 Posology and method of administration

Therapy 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 KEYTRUDA based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, 4.8 and 5.1).

MSI/MMR testing

If specified in the indication, patient selection for treatment with KEYTRUDA based on MSI-H/dMMR tumour status should be confirmed by a validated test (see sections 4.1 and 5.1).

Posology

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 3 years and older with cHL or patients aged 12 years and older with melanoma is 2 mg/kg bodyweight (bw) (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes.

For use in combination, see the Summary of Product Characteristics (SmPC) for the concomitant therapies.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity (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 for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

For the adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 4 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 13 doses of 200 mg every 3 weeks or 7 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

For the neoadjuvant and adjuvant treatment of TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

Dose delay or discontinuation (see also section 4.4)
No dose reductions of KEYTRUDA are recommended. KEYTRUDA should be withheld or discontinued to manage adverse reactions as described in Table 1.

Table 1: Recommended treatment modifications for KEYTRUDA

Immune-mediated adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis **NOTE:** for RCC patients treated with **pembrolizumab in combination with axitinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue

Immune-mediated adverse reactions	Severity	Treatment modification
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4 myocarditis Grades 3 or 4 encephalitis Grades 3 or 4 Guillain-Barré syndrome	Permanently discontinue
	Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grades 3 or 4	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v.4).

* If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, KEYTRUDA should be permanently discontinued.

The safety of re-initiating pembrolizumab therapy in patients previously experiencing immune-mediated myocarditis is not known.

KEYTRUDA, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated adverse reactions, unless otherwise specified in Table 1.

For Grade 4 haematological toxicity, only in patients with cHL, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1.

KEYTRUDA in combination with axitinib in RCC
For RCC patients treated with KEYTRUDA in combination with axitinib, see the SmPC regarding dosing of axitinib. When used in combination with pembrolizumab, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer (see section 5.1).

For liver enzyme elevations, in patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥ 3 times ULN but < 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered. If rechallenging with axitinib, dose reduction as per the axitinib SmPC may be considered.
- If ALT or AST ≥ 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered.

KEYTRUDA in combination with lenvatinib
When used in combination with lenvatinib, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued in accordance with the instructions in the lenvatinib SmPC for combination with pembrolizumab. No dose reductions are recommended for KEYTRUDA.

Patients treated with KEYTRUDA must be given the patient card and be informed about the risks of KEYTRUDA (see also package leaflet).

Special populations
Elderly
No dose adjustment is necessary in patients ≥ 65 years (see sections 4.4 and 5.1).

Renal impairment
No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is needed for patients with mild or moderate hepatic impairment. KEYTRUDA has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of KEYTRUDA in children below 18 years of age have not been established except in paediatric patients with melanoma or cHL. Currently available data are described in sections 4.8, 5.1 and 5.2.

Method of administration

KEYTRUDA is for intravenous use. It must be administered by infusion over 30 minutes. KEYTRUDA must not be administered as an intravenous push or bolus injection.

When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.

For instructions on dilution 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 chosen to minimise false negative or false positive determinations.

Immune-mediated adverse reactions
Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-mediated adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of pembrolizumab. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-mediated pneumonitis
Pneumonitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis (see section 4.2).

Immune-mediated colitis
Colitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 or recurrent Grade 3 colitis (see section 4.2). The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-mediated hepatitis
Hepatitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued (see section 4.2).

Immune-mediated nephritis
Nephritis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis (see section 4.2).

Immune-mediated endocrinopathies
Severe endocrinopathies, including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment.

Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.

Adrenal insufficiency (primary and secondary) has been reported in patients receiving pembrolizumab. Hypophysitis has also been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated. Pembrolizumab should be withheld for Grade 2 adrenal insufficiency or hypophysitis until the event is controlled with hormone replacement. Pembrolizumab should be withheld or discontinued for Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see section 4.2). Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of type 1 diabetes associated with Grade ≥ 3 hyperglycaemia or ketoacidosis until metabolic control is achieved (see section 4.2).

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued (see sections 4.2 and 4.8).

Immune-mediated skin adverse reactions
Immune-mediated severe skin reactions have been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see section 4.2).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving pembrolizumab (see section 4.8). For suspected SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued (see section 4.2).

Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anti-cancer agents.

Other immune-mediated adverse reactions
The following additional clinically significant, immune-mediated adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis noninfective and hypoparathyroidism (see sections 4.2 and 4.8).

Based on the severity and type of the adverse reaction, pembrolizumab should be withheld for Grade 2 or Grade 3 events and corticosteroids administered.

Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction.

For Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome, pembrolizumab should be permanently discontinued (see sections 4.2 and 4.8).

Transplant-related adverse reactions

Solid organ transplant rejection
Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)

Allogeneic HSCT after treatment with pembrolizumab
Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with cHL undergoing allogeneic HSCT after previous exposure to pembrolizumab. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case (see section 4.8).

Allogeneic HSCT prior to treatment with pembrolizumab
In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with pembrolizumab. Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Infusion-related reactions
Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab (see section 4.8). For Grades 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued (see section 4.2). Patients with Grades 1 or 2 infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Use of pembrolizumab in combination with chemotherapy
Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis (see section 5.1).

Disease-specific precautions

Use of pembrolizumab in urothelial carcinoma patients who have received prior platinum-containing chemotherapy
Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial carcinoma, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy (see section 5.1). Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Use of pembrolizumab in urothelial carcinoma for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10
The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit has been assessed in a comparative study (KEYNOTE-361). In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 5.1). No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy. KEYNOTE-052 also included patients eligible for mono-chemotherapy, for whom no randomised data are available. In addition, no

safety and efficacy data are available in frailer patients (e.g. ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

Use of pembrolizumab for first-line treatment of patients with NSCLC
In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components (see sections 4.2 and 4.8). A direct comparison of pembrolizumab when used in combination with chemotherapy to pembrolizumab monotherapy is not available.

Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in previously untreated patients with NSCLC whose tumours express PD-L1.

In KEYNOTE-042, a higher number of deaths within 4 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 5.1).

Use of pembrolizumab for first-line treatment of patients with HNSCC
In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components (see section 4.8).

Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in patients with HNSCC whose tumours express PD-L1 (see section 5.1).

Use of pembrolizumab for treatment of patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma
A direct comparison of pembrolizumab when used in combination with lenvatinib to pembrolizumab monotherapy is not available. Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with lenvatinib) before initiating treatment in patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma.

Use of pembrolizumab for adjuvant treatment of patients with melanoma
A trend toward increased frequency of severe and serious adverse reactions in patients ≥ 75 years was observed. Safety data of pembrolizumab in the adjuvant melanoma setting in patients ≥ 75 years are limited.

Use of pembrolizumab in combination with axitinib for first-line treatment of patients with RCC
When pembrolizumab is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. More frequent monitoring of liver enzymes as compared to when the medicines are used in monotherapy may be considered. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the SmPC for axitinib).

Use of pembrolizumab for first-line treatment of patients with MSI-H/dMMR CRC
In KEYNOTE-177, the hazard rates for overall survival events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab (see section 5.1).

Use of pembrolizumab for first-line treatment of patients with BTC
Cholangitis and biliary tract infections are not uncommon in patients with BTC. Cholangitis events were reported in KEYNOTE-966 in both treatment groups (11.2% [n=59] of participants in the

pembrolizumab plus chemotherapy arm and 10.3% [n=55] of participants in the placebo plus chemotherapy arm). Patients with biliary stents and drains (n=74) were at increased risk of cholangitis and biliary tract infections in KEYNOTE-966 (39.4% [n=13] of participants in the pembrolizumab plus chemotherapy arm vs. 29.3% [n=12] of participants in the placebo plus chemotherapy arm). Patients with BTC (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter.

Patients excluded from clinical studies
Patients with the following conditions were excluded from clinical studies: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, hepatitis B or hepatitis C infection (except for BTC); active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical studies and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (see section 5.1).

After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.

Patient card
All prescribers of KEYTRUDA must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of KEYTRUDA therapy with the patient. The patient will be provided with the patient card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-mediated adverse reactions (see section 4.4). Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Pregnancy
There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss

(see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are known to cross the placental barrier; therefore, being an IgG4, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.

Breast-feeding
It is unknown whether pembrolizumab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue pembrolizumab, taking into account the benefit of breast-feeding for the child and the benefit of pembrolizumab therapy for the woman.

Fertility
No clinical data are available on the possible effects of pembrolizumab on fertility. There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Pembrolizumab has a minor influence on the ability to drive and use machines. In some patients, dizziness and fatigue have been reported following administration of pembrolizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Pembrolizumab is most commonly associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below). The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

Pembrolizumab in monotherapy (see section 4.2)
The safety of pembrolizumab as monotherapy has been evaluated in 7 631 patients across tumour types and across four doses (2 mg/kg bw every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bw every 2 or 3 weeks) in clinical studies. In this patient population, the median observation time was 8.5 months (range: 1 day to 39 months) and the most frequent adverse reactions with pembrolizumab were fatigue (31%), diarrhoea (22%), and nausea (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-mediated adverse reactions and severe infusion-related reactions (see section 4.4). The incidences of immune-mediated adverse reactions were 37% all Grades and 9% for Grades 3-5 for pembrolizumab monotherapy in the adjuvant setting and 25% all Grades and 6% for Grades 3-5 in the metastatic setting. No new immune-mediated adverse reactions were identified in the adjuvant setting.

Pembrolizumab in combination with chemotherapy (see section 4.2)
When pembrolizumab is administered in combination, refer to the SmPC for the respective combination therapy components prior to initiation of treatment.

The safety of pembrolizumab in combination with chemotherapy has been evaluated in 5 183 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw pembrolizumab every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (52%), nausea (52%), fatigue (35%), diarrhoea (33%), constipation (32%), vomiting (28%), decreased appetite (28%), neutrophil count decreased (27%) and neutropenia (25%). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 69% for pembrolizumab combination therapy and 61% for chemotherapy alone, in patients with HNSCC were 85% for pembrolizumab combination therapy and 84% for chemotherapy plus cetuximab, in patients with oesophageal carcinoma were 86% for pembrolizumab combination therapy and 83% for chemotherapy alone, in patients with TNBC

were 80% for pembrolizumab combination therapy and 77% for chemotherapy alone, in patients with cervical cancer were 82% for pembrolizumab combination and 75% for chemotherapy, with or without bevacizumab, in patients with gastric cancer were 74% for pembrolizumab combination therapy (chemotherapy with or without trastuzumab) and 68% for chemotherapy with or without trastuzumab, and in patients with biliary tract carcinoma were 85% for pembrolizumab combination therapy and 84% for chemotherapy alone.

Pembrolizumab in combination with tyrosine kinase inhibitor (TKI) (see section 4.2)
When pembrolizumab is administered in combination with axitinib or lenvatinib, refer to the SmPC for axitinib or lenvatinib prior to initiation of treatment. For additional lenvatinib safety information related to advanced RCC see the SmPC for Kisplyx and for advanced EC see the SmPC for Lenvima. For additional axitinib safety information for elevated liver enzymes see also section 4.4.

The safety of pembrolizumab in combination with axitinib or lenvatinib in advanced RCC, and in combination with lenvatinib in advanced EC has been evaluated in a total of 1 456 patients with advanced RCC or advanced EC receiving 200 mg pembrolizumab every 3 weeks with either axitinib 5 mg twice daily or lenvatinib 20 mg once daily in clinical studies, as appropriate. In these patient populations, the most frequent adverse reactions were diarrhoea (58%), hypertension (54%), hypothyroidism (46%), fatigue (41%), decreased appetite (40%), nausea (40%), arthralgia (30%), vomiting (28%), weight decreased (28%), dysphonia (28%), abdominal pain (28%), proteinuria (27%), palmar-plantar erythrodysaesthesia syndrome (26%), rash (26%), stomatitis (25%), constipation (25%), musculoskeletal pain (23%), headache (23%) and cough (21%). Grades 3-5 adverse reactions in patients with RCC were 80% for pembrolizumab in combination with either axitinib or lenvatinib and 71% for sunitinib alone. In patients with EC, Grades 3-5 adverse reactions were 89% for pembrolizumab in combination with lenvatinib and 73% for chemotherapy alone.

Tabulated summary of adverse reactions
Adverse reactions observed in clinical studies of pembrolizumab as monotherapy or in combination with chemotherapy or other anti-tumour medicines or reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Adverse reactions known to occur with pembrolizumab or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.
For additional safety information when pembrolizumab is administered in combination, refer to the SmPC for the respective combination therapy components.

Table 2: Adverse reactions in patients treated with pembrolizumab†

	Monotherapy	**In combination with chemotherapy**	**In combination with axitinib or lenvatinib**
Infections and infestations			
Very common			urinary tract infection
Common	pneumonia	pneumonia	pneumonia
Blood and lymphatic system disorders			
Very common	anaemia	anaemia, neutropenia, thrombocytopenia	anaemia
Common	thrombocytopenia, neutropenia, lymphopenia	febrile neutropenia, leukopenia, lymphopenia	neutropenia, thrombocytopenia, lymphopenia, leukopenia
Uncommon	leukopenia, immune thrombocytopenia, eosinophilia	eosinophilia	eosinophilia

	Monotherapy	In combination with chemotherapy	In combination with axitinib or lenvatinib
Rare	haemophagocytic lymphohistiocytosis, haemolytic anaemia, pure red cell aplasia	haemolytic anaemia, immune thrombocytopenia	
Immune system disorders			
Common	infusion-related reaction*	infusion-related reaction*	infusion-related reaction*
Uncommon	sarcoidosis*		
Rare		sarcoidosis	
Not known	solid organ transplant rejection		
Endocrine disorders			
Very common	hypothyroidism*	hypothyroidism*	hypothyroidism
Common	hyperthyroidism	adrenal insufficiency*, thyroiditis*, hyperthyroidism*	adrenal insufficiency*, hyperthyroidism, thyroiditis*
Uncommon	adrenal insufficiency*, hypophysitis*, thyroiditis*	hypophysitis*	hypophysitis*
Rare	hypoparathyroidism	hypoparathyroidism	hypoparathyroidism
Metabolism and nutrition disorders			
Very common	decreased appetite	hypokalaemia, decreased appetite	decreased appetite
Common	hyponatraemia, hypokalaemia, hypocalcaemia	hyponatraemia, hypocalcaemia	hyponatraemia, hypokalaemia, hypocalcaemia
Uncommon	type 1 diabetes mellitus*	type 1 diabetes mellitus*	type 1 diabetes mellitus*
Psychiatric disorders			
Very common		insomnia	
Common	insomnia		insomnia
Nervous system disorders			
Very common	headache	neuropathy peripheral, headache	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	dizziness, dysgeusia, lethargy	dizziness, neuropathy peripheral, lethargy
Uncommon	myasthenic syndrome*, epilepsy	encephalitis*, epilepsy	myasthenic syndrome*, encephalitis*
Rare	Guillain-Barré syndrome*, encephalitis*, myelitis*, optic neuritis, meningitis (aseptic)*	myasthenic syndrome, Guillain-Barré syndrome*, optic neuritis	optic neuritis
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis*		uveitis*
Rare	Vogt-Koyanagi-Harada syndrome	uveitis*	Vogt-Koyanagi-Harada syndrome
Cardiac disorders			

	Monotherapy	**In combination with chemotherapy**	**In combination with axitinib or lenvatinib**
Common	cardiac arrhythmia‡ (including atrial fibrillation)	cardiac arrhythmia‡ (including atrial fibrillation)	cardiac arrhythmia‡ (including atrial fibrillation)
Uncommon	myocarditis, pericardial effusion, pericarditis	myocarditis*, pericardial effusion, pericarditis	myocarditis, pericardial effusion
Vascular disorders			
Very common			hypertension
Common	hypertension	hypertension	
Uncommon		vasculitis*	vasculitis*
Rare	vasculitis*		
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea, cough	dyspnoea, cough	dyspnoea, cough
Common	pneumonitis*	pneumonitis*	pneumonitis*
Gastrointestinal disorders			
Very common	diarrhoea, abdominal pain*, nausea, vomiting, constipation	diarrhoea, vomiting, nausea, abdominal pain*, constipation	diarrhoea, abdominal pain*, nausea, vomiting, constipation
Common	colitis*, dry mouth	colitis*, gastritis*, dry mouth	colitis*, pancreatitis*, gastritis*, dry mouth
Uncommon	pancreatitis*, gastritis*, gastrointestinal ulceration*	pancreatitis*, gastrointestinal ulceration*	gastrointestinal ulceration*
Rare	pancreatic exocrine insufficiency, small intestinal perforation, coeliac disease	pancreatic exocrine insufficiency, small intestinal perforation, coeliac disease	small intestinal perforation
Not known			pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders			
Common	hepatitis*	hepatitis*	hepatitis*
Rare	cholangitis sclerosing	cholangitis sclerosing*	
Skin and subcutaneous tissue disorders			
Very common	pruritus*, rash*	alopecia, pruritus*, rash*	rash*, pruritus*
Common	severe skin reactions*, erythema, dermatitis, dry skin, vitiligo*, eczema, alopecia, dermatitis acneiform	severe skin reactions*, erythema, dermatitis, dry skin, dermatitis acneiform, eczema	severe skin reactions*, dermatitis, dry skin, erythema, dermatitis acneiform, alopecia
Uncommon	psoriasis, lichenoid keratosis*, papule, hair colour changes	psoriasis, vitiligo*, papule	eczema, lichenoid keratosis*, psoriasis, vitiligo*, papule, hair colour changes

	Monotherapy	In combination with chemotherapy	In combination with axitinib or lenvatinib
Rare	Stevens-Johnson syndrome, erythema nodosum, toxic epidermal necrolysis	Stevens-Johnson syndrome, lichenoid keratosis*, erythema nodosum, hair colour changes	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain*, arthralgia	musculoskeletal pain*, arthralgia	arthralgia, musculoskeletal pain*, myositis*, pain in extremity
Common	myositis*, pain in extremity, arthritis*	myositis*, pain in extremity, arthritis*	arthritis*
Uncommon	tenosynovitis*	tenosynovitis*	tenosynovitis*
Rare	Sjogren's syndrome	Sjogren's syndrome	Sjogren's syndrome
Renal and urinary disorders			
Common		acute kidney injury	nephritis*
Uncommon	nephritis*	nephritis*, cystitis noninfective	
Rare	cystitis noninfective		cystitis noninfective
General disorders and administration site conditions			
Very common	fatigue, asthenia, oedema*, pyrexia	fatigue, asthenia, pyrexia	fatigue, asthenia, oedema*, pyrexia
Common	influenza-like illness, chills	oedema*, influenza-like illness, chills	influenza-like illness, chills
Investigations			
Very common		alanine aminotransferase increased, aspartate aminotransferase increased	lipase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased, blood creatinine increased	blood bilirubin increased, blood alkaline phosphatase increased, blood creatinine increased, hypercalcaemia	amylase increased, blood bilirubin increased, blood alkaline phosphatase increased, hypercalcaemia
Uncommon	amylase increased	amylase increased	

†Adverse reaction frequencies presented in Table 2 may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.
‡Based upon a standard query including bradyarrhythmias and tachyarrhythmias.
*The following terms represent a group of related events that describe a medical condition rather than a single event:

- infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion-related hypersensitivity reaction, cytokine release syndrome and serum sickness)
- sarcoidosis (cutaneous sarcoidosis and pulmonary sarcoidosis)
- hypothyroidism (myxoedema, immune-mediated hypothyroidism and autoimmune hypothyroidism)
- adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute and secondary adrenocortical insufficiency)
- thyroiditis (autoimmune thyroiditis, silent thyroiditis, thyroid disorder, thyroiditis acute and immune-mediated thyroiditis)
- hyperthyroidism (Basedow's disease)
- hypophysitis (hypopituitarism and lymphocytic hypophysitis)
- type 1 diabetes mellitus (diabetic ketoacidosis)
- myasthenic syndrome (myasthenia gravis, including exacerbation)
- encephalitis (autoimmune encephalitis and noninfective encephalitis)
- Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
- myelitis (including transverse myelitis)
- meningitis aseptic (meningitis and meningitis noninfective)
- uveitis (chorioretinitis, iritis and iridocyclitis)
- myocarditis (autoimmune myocarditis)
- vasculitis (central nervous system vasculitis, aortitis and giant cell arteritis)
- pneumonitis (interstitial lung disease, organising pneumonia, immune-mediated pneumonitis, immune-mediated lung disease and autoimmune lung disease)
- abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
- colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis and immune-mediated enterocolitis)
- gastritis (gastritis erosive and gastritis haemorrhagic)
- pancreatitis (autoimmune pancreatitis, pancreatitis acute and immune-mediated pancreatitis)
- gastrointestinal ulceration (gastric ulcer and duodenal ulcer)
- hepatitis (autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis)
- cholangitis sclerosing (immune-mediated cholangitis)
- pruritus (urticaria, urticaria papular and pruritus genital)
- rash (rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
- severe skin reactions (exfoliative rash, pemphigus, and Grade ≥ 3 of the following: cutaneous vasculitis, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, lichen planus, oral lichen planus, pemphigoid, pruritus, pruritus genital, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, skin necrosis and toxic skin eruption)
- vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
- lichenoid keratosis (lichen planus and lichen sclerosus)
- musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
- myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis)
- arthritis (joint swelling, polyarthritis, joint effusion, autoimmune arthritis and immune-mediated arthritis)
- tenosynovitis (tendonitis, synovitis and tendon pain)
- nephritis (autoimmune nephritis, immune-mediated nephritis, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome, glomerulonephritis, glomerulonephritis membranous and glomerulonephritis acute)
- oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema)

Description of selected adverse reactions

Data for the following immune-mediated adverse reactions are based on patients who received pembrolizumab across four doses (2 mg/kg bw every 3 weeks, 10 mg/kg bw every 2 or 3 weeks, or 200 mg every 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-mediated adverse reactions (see section 4.4)

Immune-mediated pneumonitis

Pneumonitis occurred in 324 (4.2%) patients, including Grade 2, 3, 4 or 5 cases in 143 (1.9%), 81 (1.1%), 19 (0.2%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.9 months (range: 2 days to 27.2 months). The median duration was 2.0 months (range: 1 day to 51.0+ months). Pneumonitis occurred more frequently in patients with a

history of prior thoracic radiation (8.1%) than in patients who did not receive prior thoracic radiation (3.9%). Pneumonitis led to discontinuation of pembrolizumab in 131 (1.7%) patients. Pneumonitis resolved in 196 patients, 6 with sequelae.

In patients with NSCLC, pneumonitis occurred in 230 (6.1%), including Grade 2, 3, 4 or 5 cases in 103 (2.7%), 63 (1.7%), 17 (0.4%) and 10 (0.3%), respectively. In patients with locally advanced or metastatic NSCLC, pneumonitis occurred in 8.9% with a history of prior thoracic radiation. In patients with cHL, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

Immune-mediated colitis
Colitis occurred in 158 (2.1%) patients, including Grade 2, 3 or 4 cases in 49 (0.6%), 82 (1.1%) and 6 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4.3 months (range: 2 days to 24.3 months). The median duration was 1.1 month (range: 1 day to 45.2 months). Colitis led to discontinuation of pembrolizumab in 48 (0.6%) patients. Colitis resolved in 132 patients, 2 with sequelae. In patients with CRC treated with pembrolizumab as monotherapy (n=153), the incidence of colitis was 6.5% (all Grades) with 2.0% Grade 3 and 1.3% Grade 4.

Immune-mediated hepatitis
Hepatitis occurred in 80 (1.0%) patients, including Grade 2, 3 or 4 cases in 12 (0.2%), 55 (0.7%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.5 months (range: 8 days to 26.3 months). The median duration was 1.3 months (range: 1 day to 29.0+ months). Hepatitis led to discontinuation of pembrolizumab in 37 (0.5%) patients. Hepatitis resolved in 60 patients.

Immune-mediated nephritis
Nephritis occurred in 37 (0.5%) patients, including Grade 2, 3 or 4 cases in 11 (0.1%), 19 (0.2%) and 2 (< 0.1%) patients, respectively, receiving pembrolizumab as monotherapy. The median time to onset of nephritis was 4.2 months (range: 12 days to 21.4 months). The median duration was 3.3 months (range: 6 days to 28.2+ months). Nephritis led to discontinuation of pembrolizumab in 17 (0.2%) patients. Nephritis resolved in 25 patients, 5 with sequelae. In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=488), the incidence of nephritis was 1.4% (all Grades) with 0.8% Grade 3 and 0.4% Grade 4.

Immune-mediated endocrinopathies
Adrenal insufficiency occurred in 74 (1.0%) patients, including Grade 2, 3 or 4 cases in 34 (0.4%), 31 (0.4%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5.4 months (range: 1 day to 23.7 months). The median duration was not reached (range: 3 days to 40.1+ months). Adrenal insufficiency led to discontinuation of pembrolizumab in 13 (0.2%) patients. Adrenal insufficiency resolved in 28 patients, 11 with sequelae.

Hypophysitis occurred in 52 (0.7%) patients, including Grade 2, 3 or 4 cases in 23 (0.3%), 24 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 5.9 months (range: 1 day to 17.7 months). The median duration was 3.6 months (range: 3 days to 48.1+ months). Hypophysitis led to discontinuation of pembrolizumab in 14 (0.2%) patients. Hypophysitis resolved in 23 patients, 8 with sequelae.

Hyperthyroidism occurred in 394 (5.2%) patients, including Grade 2 or 3 cases in 108 (1.4%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range: 1 day to 23.2 months). The median duration was 1.6 months (range: 4 days to 43.1+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hyperthyroidism resolved in 326 (82.7%) patients, 11 with sequelae. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2 060), the incidence of hyperthyroidism was 11.0%, the majority of which were Grade 1 or 2.

Hypothyroidism occurred in 939 (12.3%) patients, including Grade 2 or 3 cases in 687 (9.0%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.4 months (range: 1 day to 25.9 months). The median duration was not reached (range: 2 days to 63.0+ months). Hypothyroidism led to discontinuation of pembrolizumab in 6 (0.1%) patients. Hypothyroidism resolved in 216 (23.0%) patients, 16 with sequelae. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In patients with HNSCC treated with pembrolizumab as monotherapy (n=909), the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with pembrolizumab in combination with platinum and 5-FU chemotherapy (n=276), the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients treated with pembrolizumab in combination with axitinib or lenvatinib (n=1 456), the incidence of hypothyroidism was 46.2% (all Grades) with 0.8% Grade 3 or 4. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2 060), the incidence of hypothyroidism was 18.5%, the majority of which were Grade 1 or 2.

Immune-mediated skin adverse reactions
Immune-mediated severe skin reactions occurred in 130 (1.7%) patients, including Grade 2, 3, 4 or 5 cases in 11 (0.1%), 103 (1.3%), 1 (< 0.1%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.8 months (range: 2 days to 25.5 months). The median duration was 1.9 months (range: 1 day to 47.1+ months). Severe skin reactions led to discontinuation of pembrolizumab in 18 (0.2%) patients. Severe skin reactions resolved in 95 patients, 2 with sequelae.

Rare cases of SJS and TEN, some of them with fatal outcome, have been observed (see sections 4.2 and 4.4).

Complications of allogeneic HSCT in cHL
Of 14 patients in KEYNOTE-013 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients reported acute GVHD and 1 patient reported chronic GVHD, none of which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant.

Of 32 patients in KEYNOTE-087 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 16 patients reported acute GVHD and 7 patients reported chronic GVHD, two of which were fatal. No patients experienced hepatic VOD. No patients experienced engraftment syndrome post-transplant.

Of 14 patients in KEYNOTE-204 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant.

Elevated liver enzymes when pembrolizumab is combined with axitinib in RCC
In a clinical study of previously untreated patients with RCC receiving pembrolizumab in combination with axitinib, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT > 3 times ULN, and of those patients with recurrence of ALT > 3 times ULN, all recovered. There were no Grade 5 hepatic events.

Laboratory abnormalities
In patients treated with pembrolizumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9.4% for lymphocytes decreased, 7.4% for sodium decreased, 5.8% for haemoglobin decreased, 5.3% for phosphate

decreased, 5.3% for glucose increased, 3.3% for ALT increased, 3.1% for AST increased, 2.6% for alkaline phosphatase increased, 2.3% for potassium decreased, 2.1% for potassium increased, 1.9% for neutrophils decreased, 1.8% for platelets decreased, 1.8% for calcium increased, 1.7% for bilirubin increased, 1.5% for calcium decreased, 1.4% for albumin decreased, 1.3% for creatinine increased, 1.2% for glucose decreased, 0.8% for leucocytes decreased, 0.7% for magnesium increased, 0.5% for sodium increased, 0.4% for haemoglobin increased, and 0.2% for magnesium decreased.

In patients treated with pembrolizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 39.9% for neutrophils decreased, 25.5% for lymphocytes decreased, 23.3% for leucocytes decreased, 20.8% for haemoglobin decreased, 13.7% for platelets decreased, 10.4% for sodium decreased, 7.7% for potassium decreased, 7.3% for phosphate decreased, 5.7% for ALT increased, 5.5% for glucose increased, 5.3% for AST increased, 3.6% for bilirubin increased, 3.5% for calcium decreased, 3.4% for potassium increased, 3.1% for creatinine increased, 2.8% for alkaline phosphatase increased, 2.6% for albumin decreased, 1.7% for calcium increased, 1.0% for glucose decreased, 0.5% for sodium increased and 0.1% for haemoglobin increased.

In patients treated with pembrolizumab in combination with axitinib or lenvatinib, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 23.0% for lipase increased (not measured in patients treated with pembrolizumab and axitinib), 12.0% for lymphocyte decreased, 11.4% for sodium decreased, 11.2% for amylase increased, 11.2% for triglycerides increased, 10.4% for ALT increased, 8.9% for AST increased, 7.8% for glucose increased, 6.8% for phosphate decreased, 6.1% for potassium decreased, 5.1% for potassium increased, 4.5% for cholesterol increased, 4.4% for creatinine increased, 4.2% for haemoglobin decreased, 4.0% for magnesium decreased, 3.5% for neutrophils decreased, 3.1% for alkaline phosphatase increased, 3.0% for platelets decreased, 2.8% for bilirubin increased, 2.2% for calcium decreased, 1.7% for white blood cells decreased, 1.6% for magnesium increased, 1.5% for prothrombin INR increased, 1.4% for glucose decreased, 1.2% for albumin decreased, 1.2% for calcium increased, 0.4% for sodium increased, and 0.1% for haemoglobin increased.

Immunogenicity
In clinical studies in patients treated with pembrolizumab 2 mg/kg bw every three weeks, 200 mg every three weeks, or 10 mg/kg bw every two or three weeks as monotherapy, 36 (1.8%) of 2 034 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development.

Paediatric population
The safety of pembrolizumab as monotherapy has been evaluated in 161 paediatric patients aged 9 months to 17 years with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours at 2 mg/kg bw every 3 weeks in the Phase I/II study KEYNOTE-051. The cHL population (n=22) included patients 11 to 17 years of age. The safety profile in paediatric patients was generally similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia (33%), vomiting (30%), headache (26%), abdominal pain (22%), anaemia (21%), cough (21%) and constipation (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. Seventy-six (47.2%) patients had 1 or more Grades 3 to 5 adverse reactions of which 5 (3.1%) patients had 1 or more adverse reactions that resulted in death. The frequencies are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. Long-term safety data of pembrolizumab in adolescents with Stage IIB, IIC and III melanoma treated in the adjuvant setting are currently unavailable.

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

There is no information on overdose with pembrolizumab.

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, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF02

Mechanism of action
KEYTRUDA is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

The anti-angiogenic effect of lenvatinib (multi-TKI) in combination with the immune-stimulatory effect of pembrolizumab (anti-PD-1) results in a tumour microenvironment with greater T-cell activation to help overcome primary and acquired resistance to immunotherapy and may improve tumour responses compared to either treatment alone. In preclinical murine models, PD-1 plus TKI inhibitors have demonstrated enhanced anti-tumour activity compared to either agent alone.

Clinical efficacy and safety
Pembrolizumab doses of 2 mg/kg bw every 3 weeks, 10 mg/kg bw every 3 weeks, and 10 mg/kg bw every 2 weeks were evaluated in melanoma or previously treated NSCLC clinical studies. Based on the modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg every 3 weeks, 2 mg/kg bw every 3 weeks, and 400 mg every 6 weeks (see section 4.2).

Melanoma
KEYNOTE-006: Controlled study in melanoma patients naïve to treatment with ipilimumab
The safety and efficacy of pembrolizumab were investigated in KEYNOTE-006, a multicentre, open-label, controlled, Phase III study for the treatment of advanced melanoma in patients who were naïve to ipilimumab. Patients were randomised (1:1:1) to receive pembrolizumab 10 mg/kg bw every 2 (n=279) or 3 weeks (n=277) or ipilimumab 3 mg/kg bw every 3 weeks (n=278). Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter.

Of the 834 patients, 60% were male, 44% were ≥ 65 years (median age was 62 years [range: 18-89]) and 98% were white. Sixty-five percent of patients had M1c stage, 9% had a history of brain metastases, 66% had no and 34% had one prior therapy. Thirty-one percent had an ECOG Performance Status of 1, 69% had ECOG Performance Status of 0 and 32% had elevated LDH. BRAF

mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumours, 139 (46%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measures were progression-free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) and overall survival (OS). Secondary efficacy outcome measures were objective response rate (ORR) and response duration. Table 3 summarises key efficacy measures in patients naïve to treatment with ipilimumab at the final analysis performed after a minimum of 21 months of follow-up. Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 1 and 2.

Table 3: Efficacy results in KEYNOTE-006

Endpoint	**Pembrolizumab 10 mg/kg bw every 3 weeks n=277**	**Pembrolizumab 10 mg/kg bw every 2 weeks n=279**	**Ipilimumab 3 mg/kg bw every 3 weeks n=278**
OS			
Number (%) of patients with event	119 (43%)	122 (44%)	142 (51%)
Hazard ratio* (95% CI)	0.68 (0.53, 0.86)	0.68 (0.53, 0.87)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	Not reached (24, NA)	Not reached (22, NA)	16 (14, 22)
PFS			
Number (%) of patients with event	183 (66%)	181 (65%)	202 (73%)
Hazard ratio* (95% CI)	0.61 (0.50, 0.75)	0.61 (0.50, 0.75)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	4.1 (2.9, 7.2)	5.6 (3.4, 8.2)	2.8 (2.8, 2.9)
Best objective response			
ORR % (95% CI)	36% (30, 42)	37% (31, 43)	13% (10, 18)
Complete response	13%	12%	5%
Partial response	23%	25%	8%
Response duration‡			
Median in months (range)	Not reached (2.0, 22.8+)	Not reached (1.8, 22.8+)	Not reached (1.1+, 23.8+)
% ongoing at 18 months	68%§	71%§	70%§

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

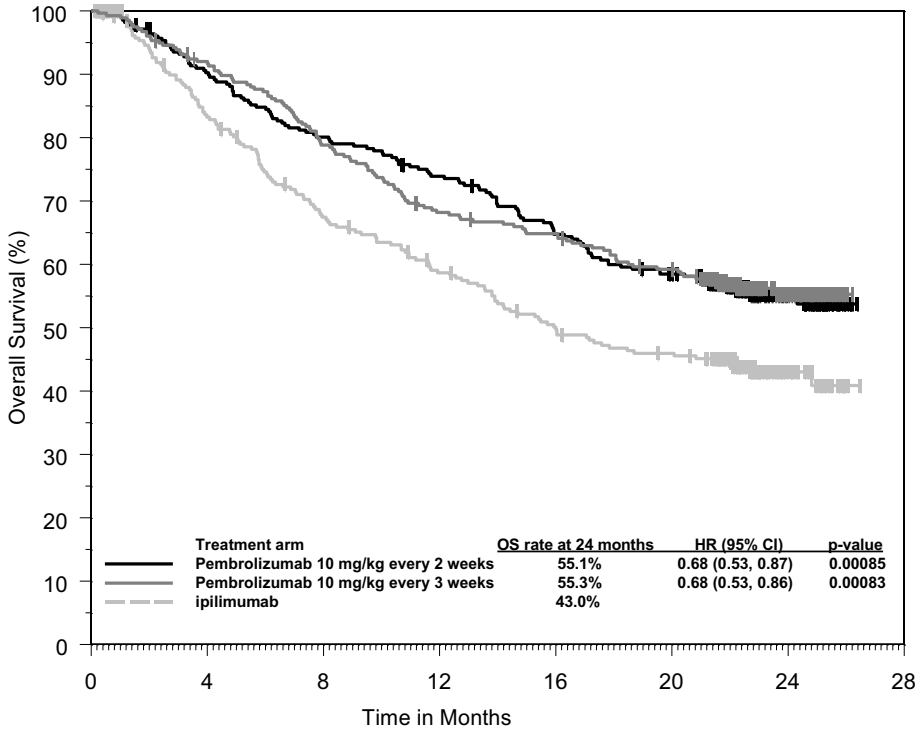
† Based on stratified log-rank test

‡ Based on patients with a best objective response as confirmed complete or partial response

§ Based on Kaplan-Meier estimation

NA = not available

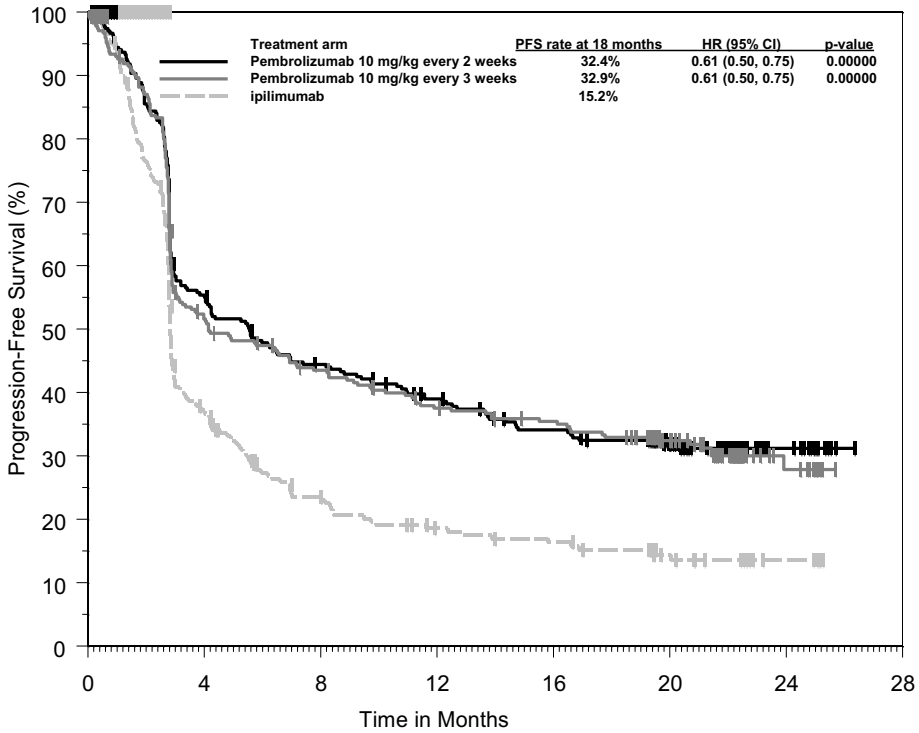
Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

Pembrolizumab 10 mg/kg every 2 weeks:	279	249	221	202	176	156	44	0
Pembrolizumab 10 mg/kg every 3 weeks:	277	251	215	184	174	156	43	0
ipilimumab:	278	213	170	145	122	110	28	0

Figure 2: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

Pembrolizumab 10 mg/kg every 2 weeks:	279	148	116	98	82	52	16	0
Pembrolizumab 10 mg/kg every 3 weeks:	277	136	111	91	84	60	13	0
ipilimumab:	278	88	48	34	29	16	5	0

KEYNOTE-002: Controlled study in melanoma patients previously treated with ipilimumab

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-002, a multicentre, double-blind, controlled study for the treatment of advanced melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=180) or 10 mg/kg bw (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; further exclusion criteria were a history of severe or life-threatening immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; ongoing adverse reactions ≥ Grade 2 from previous treatment with ipilimumab; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, hepatitis B or hepatitis C infection and ECOG Performance Status ≥ 2.

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently-verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg bw or 10 mg/kg bw of pembrolizumab every 3 weeks in a double-blind fashion.

Of the 540 patients, 61% were male, 43% were ≥ 65 years (median age was 62 years [range: 15-89]) and 98% were white. Eighty-two percent had M1c stage, 73% had at least two and 32% of patients had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG Performance Status of 1, 40% had elevated LDH and 23% had a BRAF mutated tumour.

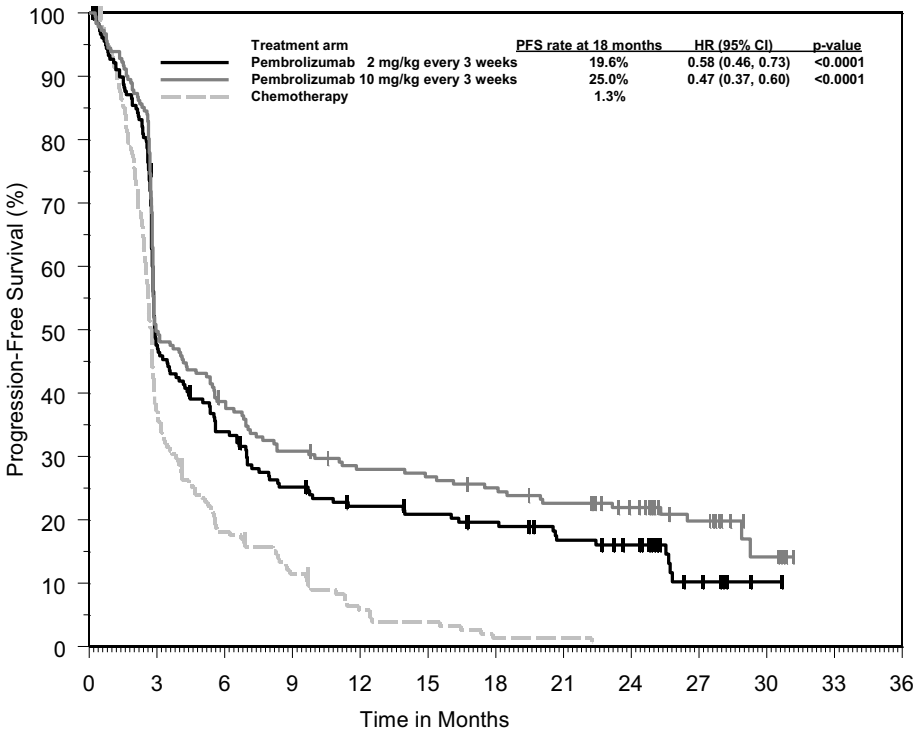
The primary efficacy outcome measures were PFS as assessed by IRO using RECIST version 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration. Table 4 summarises key efficacy measures at the final analysis in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 3. Both pembrolizumab arms were superior to chemotherapy for PFS, and there was no difference between pembrolizumab doses. There was no statistically significant difference between pembrolizumab and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomised to the chemotherapy arm, 55% crossed over and subsequently received treatment with pembrolizumab.

Table 4: Efficacy results in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks n=180	Pembrolizumab 10 mg/kg bw every 3 weeks n=181	Chemotherapy n=179
PFS			
Number (%) of patients with event	150 (83%)	144 (80%)	172 (96%)
Hazard ratio* (95% CI)	0.58 (0.46, 0.73)	0.47 (0.37, 0.60)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	3.0 (2.8, 5.2)	2.8 (2.6, 2.8)
OS			
Number (%) of patients with event	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value†	0.1173	0.0106‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Best objective response			
ORR % (95% CI)	22% (16, 29)	28% (21, 35)	5% (2, 9)
Complete response	3%	7%	0%
Partial response	19%	20%	5%
Response duration§			
Median in months (range)	22.8 (1.4+, 25.3+)	Not reached (1.1+, 28.3+)	6.8 (2.8, 11.3)
% ongoing at 12 months	73%¶	79%¶	0%¶

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Not statistically significant after adjustment for multiplicity
§ Based on patients with a best objective response as confirmed complete or partial response from the final analysis
¶ Based on Kaplan-Meier estimation

Figure 3: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-002 (intent to treat population)



Number at Risk							
Pembrolizumab 2 mg/kg every 3 weeks:	180	59	36	29	19	1	0
Pembrolizumab 10 mg/kg every 3 weeks:	181	69	48	42	30	5	0
Chemotherapy:	179	31	9	2	1	0	0

KEYNOTE-001: Open-label study in melanoma patients naïve and previously treated with ipilimumab

The safety and efficacy of pembrolizumab for patients with advanced melanoma were investigated in an uncontrolled, open-label study, KEYNOTE-001. Efficacy was evaluated for 276 patients from two defined cohorts, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor) and the other which included patients naïve to treatment with ipilimumab. Patients were randomly assigned to receive pembrolizumab at a dose of 2 mg/kg bw every 3 weeks or 10 mg/kg bw every 3 weeks. Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Exclusion criteria were similar to those of KEYNOTE-002.

Of the 89 patients receiving 2 mg/kg bw of pembrolizumab who were previously treated with ipilimumab, 53% were male, 33% were ≥ 65 years of age and the median age was 59 years (range: 18-88). All but two patients were white. Eighty-four percent had M1c stage and 8% of patients had a history of brain metastases. Seventy percent had at least two and 35% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population. All patients with BRAF mutant tumours were previously treated with a BRAF inhibitor.

Of the 51 patients receiving 2 mg/kg bw of pembrolizumab who were naïve to treatment with ipilimumab, 63% were male, 35% were ≥ 65 years of age and the median age was 60 years (range: 35-80). All but one patient was white. Sixty-three percent had M1c stage and 2% of patients had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 20 (39%) patients. Among patients with BRAF mutant tumours, 10 (50%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measure was ORR as assessed by independent review using RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS and OS. Tumour

response was assessed at 12 week intervals. Table 5 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving pembrolizumab at a dose of 2 mg/kg bw based on a minimum follow-up time of 30 months for all patients.

Table 5: Efficacy results in KEYNOTE-001

Endpoint	**Pembrolizumab 2 mg/kg bw every 3 weeks in patients previously treated with ipilimumab n=89**	**Pembrolizumab 2 mg/kg bw every 3 weeks in patients naïve to treatment with ipilimumab n=51**
Best objective response[*] by IRO[†]		
ORR % (95% CI)	26% (17, 36)	35% (22, 50)
Complete response	7%	12%
Partial response	19%	24%
Disease control rate %[‡]	48%	49%
Response duration[§]		
Median in months (range)	30.5 (2.8+, 30.6+)	27.4 (1.6+, 31.8+)
% ongoing at 24 months[¶]	75%	71%
PFS		
Median in months (95% CI)	4.9 (2.8, 8.3)	4.7 (2.8, 13.8)
PFS rate at 12 months	34%	38%
OS		
Median in months (95% CI)	18.9 (11, not available)	28.0 (14, not available)
OS rate at 24 months	44%	56%

[*] Includes patients without measurable disease at baseline by independent radiology
[†] IRO = Integrated radiology and oncologist assessment using RECIST 1.1
[‡] Based on best response of stable disease or better
[§] Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab
[¶] Based on Kaplan-Meier estimation

Results for patients previously treated with ipilimumab (n=84) and naïve to treatment with ipilimumab (n=52) who received 10 mg/kg bw of pembrolizumab every 3 weeks were similar to those seen in patients who received 2 mg/kg bw of pembrolizumab every 3 weeks.

Sub-population analyses

BRAF mutation status in melanoma

A subgroup analysis was performed as part of the final analysis of KEYNOTE-002 in patients who were BRAF wild type (n=414; 77%) or BRAF mutant with prior BRAF treatment (n=126; 23%) as summarised in Table 6.

Table 6: Efficacy results by BRAF mutation status in KEYNOTE-002

	BRAF wild type		BRAF mutant with prior BRAF treatment	
Endpoint	**Pembrolizumab 2 mg/kg bw every 3 weeks (n=136)**	**Chemotherapy (n=137)**	**Pembrolizumab 2 mg/kg bw every 3 weeks (n=44)**	**Chemotherapy (n=42)**
PFS Hazard ratio* (95% CI)	0.50 (0.39, 0.66)	---	0.79 (0.50, 1.25)	---
OS Hazard ratio* (95% CI)	0.78 (0.58, 1.04)	---	1.07 (0.64, 1.78)	---
ORR %	26%	6%	9%	0%

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type (n=525; 63%), BRAF mutant without prior BRAF treatment (n=163; 20%) and BRAF mutant with prior BRAF treatment (n=139; 17%) as summarised in Table 7.

Table 7: Efficacy results by BRAF mutation status in KEYNOTE-006

	BRAF wild type		BRAF mutant without prior BRAF treatment		BRAF mutant with prior BRAF treatment	
Endpoint	**Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)**	**Ipilimumab (n=170)**	**Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)**	**Ipilimumab (n=55)**	**Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)**	**Ipilimumab (n=52)**
PFS Hazard ratio* (95% CI)	0.61 (0.49, 0.76)	---	0.52 (0.35, 0.78)	---	0.76 (0.51, 1.14)	---
OS Hazard ratio* (95% CI)	0.68 (0.52, 0.88)	---	0.70 (0.40, 1.22)	---	0.66 (0.41, 1.04)	---
ORR %	38%	14%	41%	15%	24%	10%

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

PD-L1 status in melanoma

A subgroup analysis was performed as part of the final analysis of KEYNOTE-002 in patients who were PD-L1 positive (PD-L1 expression in ≥ 1% of tumour and tumour-associated immune cells relative to all viable tumour cells – MEL score) vs. PD-L1 negative. PD-L1 expression was tested retrospectively by immunohistochemistry (IHC) assay with the 22C3 anti-PD-L1 antibody. Among patients who were evaluable for PD-L1 expression (79%), 69% (n=294) were PD-L1 positive and 31% (n=134) were PD-L1 negative. Table 8 summarises efficacy results by PD-L1 expression.

Table 8: Efficacy results by PD-L1 expression in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks	Chemotherapy	Pembrolizumab 2 mg/kg bw every 3 weeks	Chemotherapy
	PD-L1 positive		PD-L1 negative	
PFS Hazard ratio* (95% CI)	0.55 (0.40, 0.76)	---	0.81 (0.50, 1.31)	---
OS Hazard ratio* (95% CI)	0.90 (0.63, 1.28)	---	1.18 (0.70, 1.99)	---
ORR %	25%	4%	10%	8%

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive (n=671; 80%) vs. PD-L1 negative (n=150; 18%). Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. Table 9 summarises efficacy results by PD-L1 expression.

Table 9: Efficacy results by PD-L1 expression in KEYNOTE-006

Endpoint	Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)	Ipilimumab	Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)	Ipilimumab
	PD-L1 positive		PD-L1 negative	
PFS Hazard ratio* (95% CI)	0.53 (0.44, 0.65)	---	0.87 (0.58, 1.30)	---
OS Hazard ratio* (95% CI)	0.63 (0.50, 0.80)	---	0.76 (0.48, 1.19)	---
ORR %	40%	14%	24%	13%

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

Ocular melanoma

In 20 subjects with ocular melanoma included in KEYNOTE-001, no objective responses were reported; stable disease was reported in 6 patients.

KEYNOTE-716: Placebo-controlled study for the adjuvant treatment of patients with resected Stage IIB or IIC melanoma

The efficacy of pembrolizumab was evaluated in KEYNOTE-716, a multicentre, randomised, double-blind, placebo-controlled study in patients with resected Stage IIB or IIC melanoma. A total of 976 patients were randomised (1:1) to receive pembrolizumab 200 mg every three weeks (or the paediatric [12 to 17 years old] dose of 2 mg/kg intravenously [up to a maximum of 200 mg] every three weeks) (n=487) or placebo (n=489), for up to one year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer (AJCC) 8th edition T stage. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients who received prior therapy for melanoma other than surgery were ineligible. Patients underwent imaging every six months from randomisation through the 4th year, and then once in year 5 from randomisation or until recurrence, whichever came first.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range: 16-87; 39% age 65 or older; 2 adolescent patients [one per treatment arm]); 60% male; and ECOG PS of 0 (93%) and 1 (7%). Sixty-four percent had Stage IIB and 35% had Stage IIC.

The primary efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population, where RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurred first. The secondary outcome measures were distant metastasis-free survival (DMFS) and OS in the whole population. OS was not formally assessed at the time of this analysis. The study initially demonstrated

a statistically significant improvement in RFS (HR 0.65; 95% CI 0.46, 0.92; p-Value = 0.00658) for patients randomised to the pembrolizumab arm compared with placebo at its pre-specified interim analysis. Results reported from the pre-specified final analysis for RFS at a median follow-up of 20.5 months are summarised in Table 10. Updated RFS results at a median follow-up of 38.5 months were consistent with the final analysis for RFS for patients randomised to the pembrolizumab arm compared with placebo (HR 0.62; 95% CI 0.49, 0.79) (see Figure 4). The study demonstrated a statistically significant improvement in DMFS (HR 0.64; 95% CI 0.47, 0.88; p-Value = 0.00292) for patients randomised to the pembrolizumab arm compared with placebo at its pre-specified interim analysis at a median follow-up of 26.9 months. Results reported from the pre-specified final analysis for DMFS at a median follow-up time of 38.5 months are summarised in Table 10 and Figure 5.

Table 10: Efficacy results in KEYNOTE-716

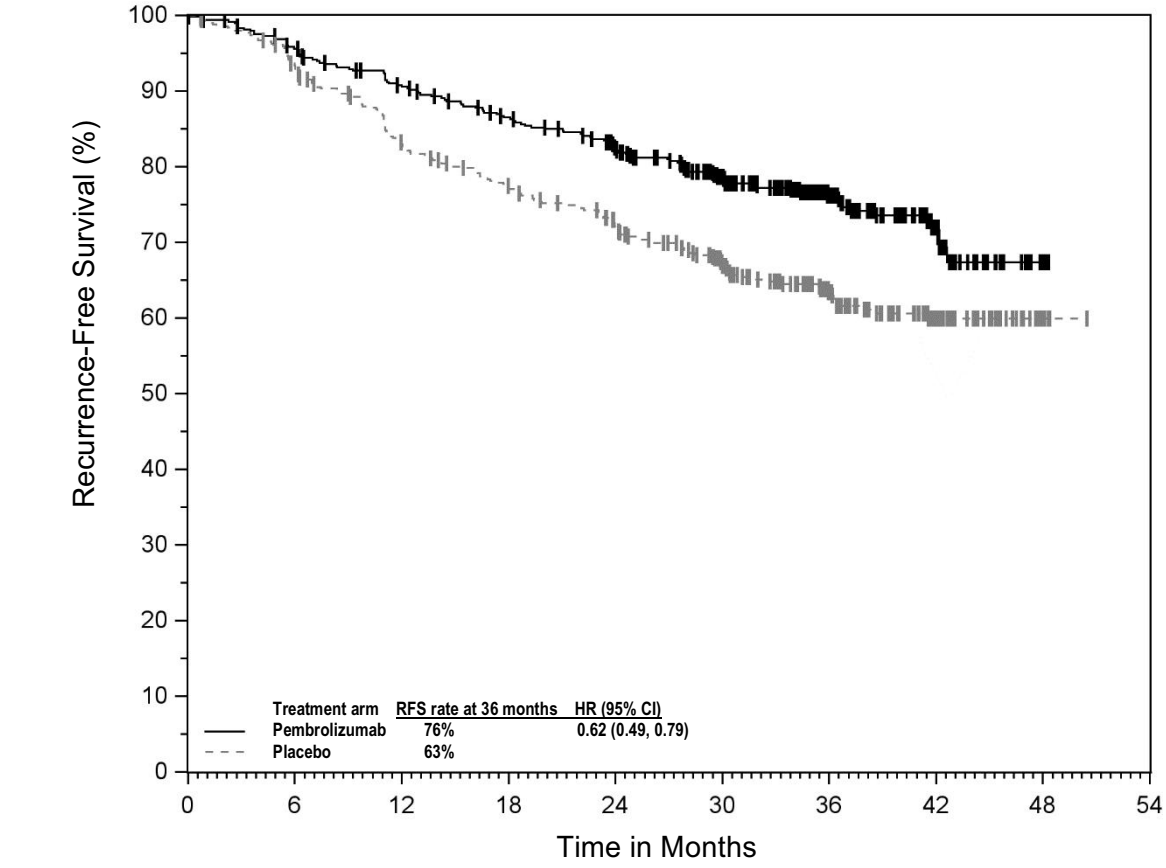
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=487**	**Placebo n=489**
RFS		
Number (%) of patients with event	72 (15%)	115 (24%)
Median in months (95% CI)	NR (NR, NR)	NR (29.9, NR)
Hazard ratio* (95% CI)	0.61 (0.45, 0.82)	
p-Value (stratified log-rank)†	0.00046	
DMFS		
Number (%) of patients with event	74 (15.2%)	119 (24.3%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.59 (0.44, 0.79)	

* Based on the stratified Cox proportional hazard model

† Nominal p-Value based on log-rank test stratified by American Joint Committee on Cancer (AJCC) 8th edition T stage.

NR = not reached

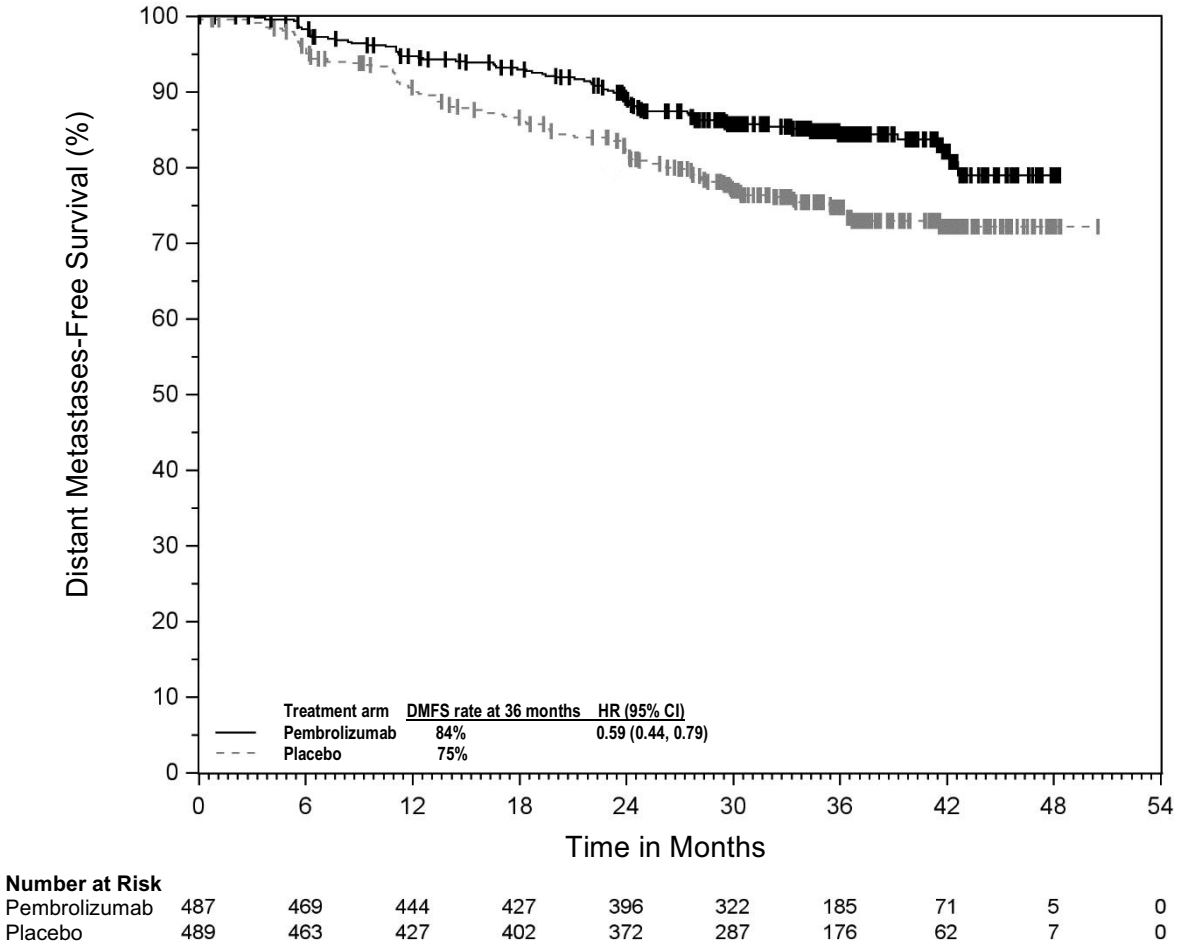
Figure 4: Kaplan-Meier curve for recurrence-free survival by treatment arm in KEYNOTE-716 (intent to treat population)



Number at Risk

Pembrolizumab	487	457	426	400	371	300	173	62	4	0
Placebo	489	452	395	363	331	252	149	51	7	0

Figure 5: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-716 (intent to treat population)



KEYNOTE-054: Placebo-controlled study for the adjuvant treatment of patients with completely resected Stage III melanoma

The efficacy of pembrolizumab was evaluated in KEYNOTE-054, a multicentre, randomised, double-blind, placebo-controlled study in patients with completely resected stage IIIA (> 1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1 019 adult patients were randomised (1:1) to receive pembrolizumab 200 mg every three weeks (n=514) or placebo (n=505), for up to one year until disease recurrence or unacceptable toxicity. Randomisation was stratified by AJCC 7th edition stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes) and geographic region (North America, European countries, Australia and other countries as designated). Patients must have undergone lymph node dissection, and if indicated, radiotherapy within 13 weeks prior to starting treatment. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients who received prior therapy for melanoma other than surgery or interferon for thick primary melanomas without evidence of lymph node involvement were ineligible. Patients underwent imaging every 12 weeks after the first dose of pembrolizumab for the first two years, then every 6 months from year 3 to 5, and then annually.

Among the 1 019 patients, the baseline characteristics were: median age of 54 years (25% age 65 or older); 62% male; and ECOG PS of 0 (94%) and 1 (6%). Sixteen percent had stage IIIA; 46% had stage IIIB; 18% had stage IIIC (1-3 positive lymph nodes) and 20% had stage IIIC (≥ 4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type. PD-L1 expression was tested retrospectively by IHC assay with the 22C3 anti-PD-L1 antibody; 84% of patients had

PD-L1-positive melanoma (PD-L1 expression in ≥ 1% of tumour and tumour-associated immune cells relative to all viable tumour cells). The same scoring system was used for metastatic melanoma (MEL score).

The primary efficacy outcome measures were investigator-assessed RFS in the whole population and in the population with PD-L1 positive tumours, where RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurred first. The secondary outcome measures were DMFS and OS in the whole population and in the population with PD-L1 positive tumours. OS was not formally assessed at the time of these analyses. The study initially demonstrated a statistically significant improvement in RFS (HR 0.57; 98.4% CI 0.43, 0.74; p-Value < 0.0001) for patients randomised to the pembrolizumab arm compared with placebo at its pre-specified interim analysis. Updated efficacy results with a median follow-up time of 45.5 months are summarised in Table 11 and Figures 6 and 7.

Table 11: Efficacy results in KEYNOTE-054

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=514**	**Placebo n=505**
RFS		
Number (%) of patients with event	203 (40%)	288 (57%)
Median in months (95% CI)	NR	21.4 (16.3, 27.0)
Hazard ratio* (95% CI)	0.59 (0.49, 0.70)	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
Median in months (95% CI)	NR	40.0 (27.7, NR)
Hazard ratio* (95% CI)	0.60 (0.49, 0.73)	
p-Value (stratified log-rank)	< 0.0001	

* Based on the stratified Cox proportional hazard model
NR = not reached

Figure 6: Kaplan-Meier curve for recurrence-free survival by treatment arm in KEYNOTE-054 (intent to treat population)

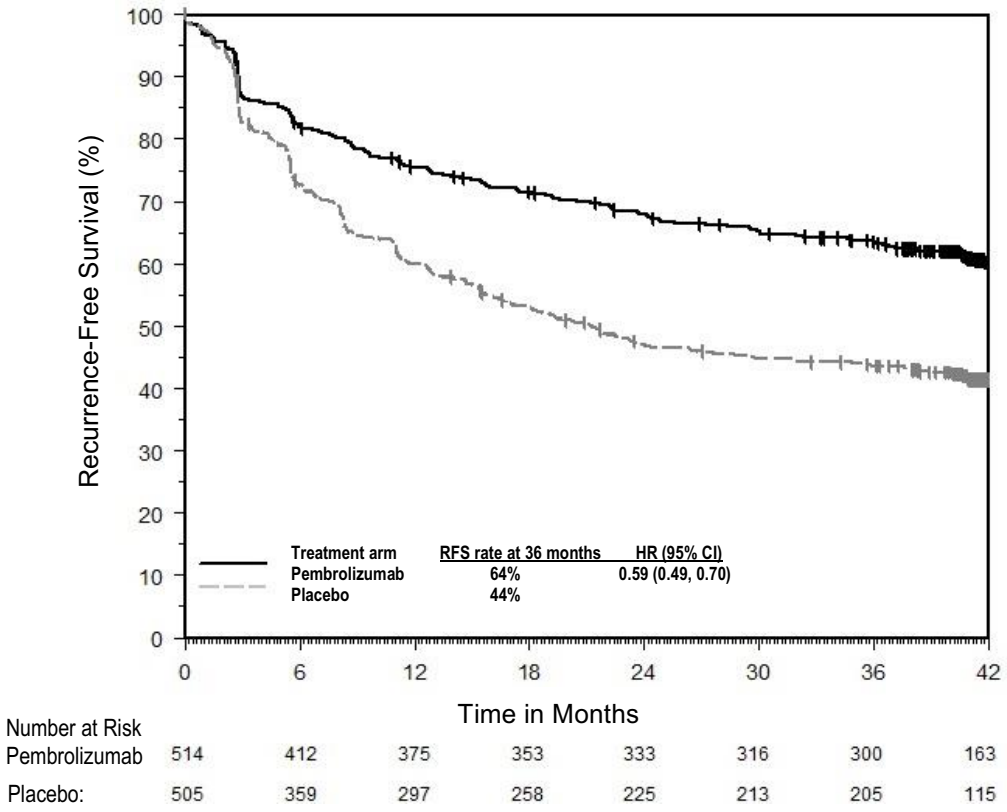
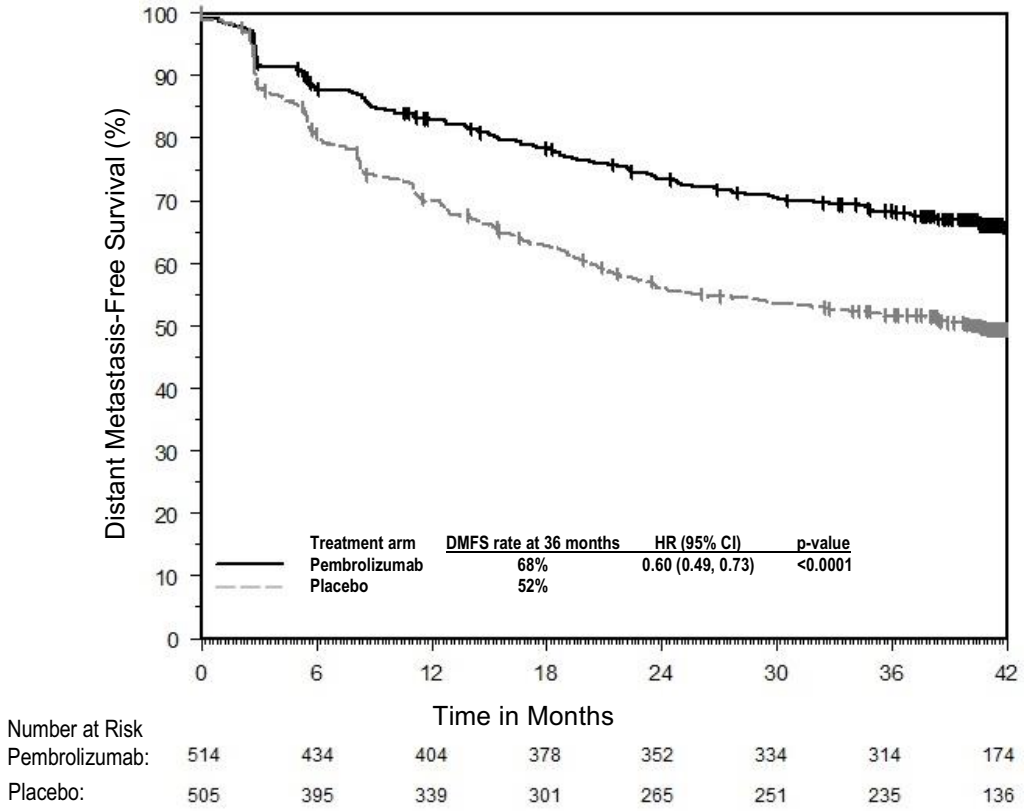


Figure 7: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-054 (intent to treat population)



RFS and DMFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF mutation status, and stage of disease (using AJCC 7th edition). These results were consistent when reclassified in a post-hoc analysis according to the current AJCC 8th edition staging system.

NSCLC

KEYNOTE-671: Controlled study for the neoadjuvant and adjuvant treatment of patients with resectable NSCLC

The efficacy of pembrolizumab in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy as adjuvant treatment was investigated in KEYNOTE-671, a multicentre, randomised, double-blind, placebo-controlled study. Key eligibility criteria were previously untreated and resectable patients with NSCLC who are at high risk (Stage II, IIIA, or IIIB (N2) by AJCC 8th edition) of recurrence, regardless of tumour PD-L1 expression based on the PD-L1 IHC 22C3 pharmDx™ Kit. Testing for genomic tumour aberrations or oncogenic drivers was not mandatory for enrolment.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with Stage II – IIIB (N2) according to the 8th edition staging system: tumour size > 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that invade thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve a mainstem bronchus with tumour > 4 cm; or tumours > 4 cm that cause obstructive atelectasis that extends to the hilum; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary lung cancer.

If indicated, patients received adjuvant radiation therapy prior to adjuvant pembrolizumab or placebo. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by stage (II vs. III), tumour PD-L1 expression (TPS ≥ 50% or < 50%), histology (squamous vs. non- squamous), and geographic region (East Asia vs. non-East Asia).

Patients were randomised (1:1) to one of the following treatment arms:

- Treatment Arm A: neoadjuvant pembrolizumab 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1 000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, pembrolizumab 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1 000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with pembrolizumab or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumour status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase, and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumour status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The primary efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Secondary efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review (BIPR).

A total of 797 patients in KEYNOTE-671 were randomised: 397 patients to the pembrolizumab arm and 400 to the placebo arm. Baseline characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older; 71% male; 61% White, 31% Asian, and 2% Black. Sixty-three percent and 37% had ECOG performance of 0 or 1, respectively; 30% had Stage II and 70% had Stage III disease; 33% had TPS ≥ 50% and 67% had TPS < 50%; 43% had tumours with squamous histology and 57% had tumours with non-squamous histology; 31% were from the East Asian region. Four percent of patients had EGFR mutations and in 66% EGFR mutation status was unknown. Three percent of patients had ALK translocations and in 68% ALK translocation status was unknown.

Eighty-one percent of patients in the pembrolizumab in combination with platinum-containing chemotherapy arm had definitive surgery compared to 76% of patients in the platinum-containing chemotherapy arm.

The study demonstrated statistically significant improvements in OS, EFS, pCR and mPR for patients randomised to pembrolizumab in combination with platinum-containing chemotherapy followed by pembrolizumab monotherapy compared with patients randomised to placebo in combination with platinum-containing chemotherapy followed by placebo alone. At a pre-specified interim analysis (median follow-up time of 21.4 months (range: 0.4 to 50.6 months)) the EFS HR was 0.58 (95% CI: 0.46, 0.72; p < 0.0001) for patients randomised to pembrolizumab in combination with platinum-containing chemotherapy followed by pembrolizumab monotherapy compared with patients randomised to placebo in combination with platinum-containing chemotherapy followed by placebo alone. At the time of this analysis, OS results were not mature.

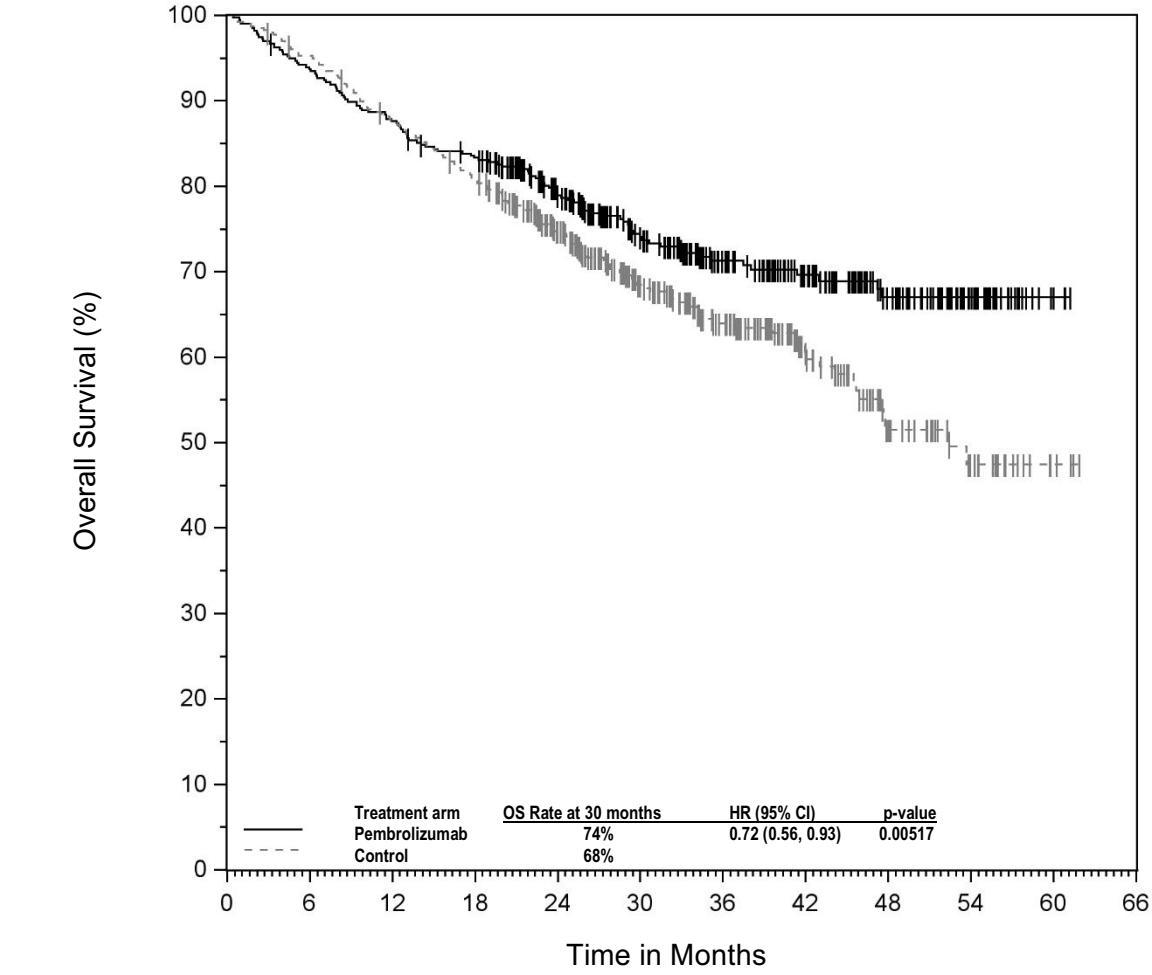
Table 12 summarises key efficacy measures at a pre-specified interim analysis at a median follow-up time of 29.8 months (range: 0.4 to 62.0 months). The Kaplan-Meier curves for OS and EFS are shown in Figures 8 and 9.

Table 12: Efficacy results in KEYNOTE-671

Endpoint	**Pembrolizumab with chemotherapy/ Pembrolizumab n=397**	**Placebo with chemotherapy/ Placebo n=400**
OS		
Number (%) of patients with event	110 (28%)	144 (36%)
Median in months* (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.93)	
p-Value‡	0.00517	
EFS		
Number (%) of patients with event	174 (44%)	248 (62%)
Median in months* (95% CI)	47.2 (32.9, NR)	18.3 (14.8, 22.1)
Hazard ratio† (95% CI)	0.59 (0.48, 0.72)	

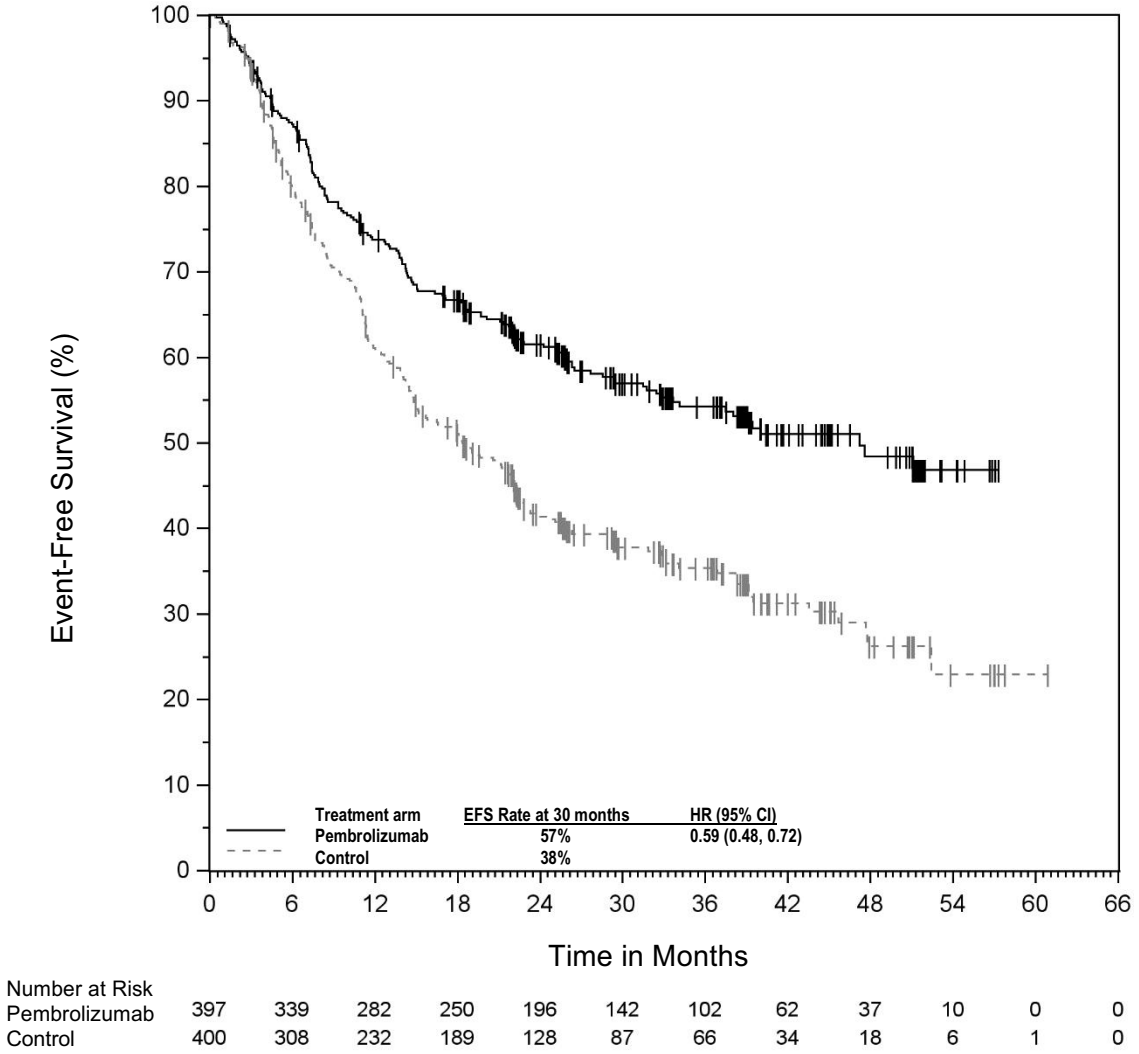
* Based on Kaplan-Meier estimates
† Based on Cox regression model with treatment as a covariate stratified by stage, tumour PD-L1 expression, histology, and geographic region
‡ Based on stratified log-rank test
NR = not reached

Figure 8: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-671 (intent to treat population)



Number at Risk												
Pembrolizumab	397	371	347	327	277	205	148	108	69	32	4	0
Control	400	379	347	319	256	176	125	77	39	20	4	0

Figure 9: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-671 (intent to treat population)



A post-hoc exploratory subgroup analysis was performed in KEYNOTE-671 in patients who had PD-L1 TPS ≥ 50% (pembrolizumab arm [n=132; 33%] vs. placebo arm [n=134; 34%]); TPS = 1 - 49% (pembrolizumab arm [n=127; 32%] vs. placebo arm [n=115; 29%]) and TPS < 1% (pembrolizumab arm [n=138; 35%] vs. placebo arm [n=151; 38%]). The EFS HR was, 0.48 (95% CI: 0.33, 0.71) in patients with a TPS ≥ 50%, 0.52 (95% CI: 0.36, 0.73) in patients with a TPS = 1 - 49% and 0.75 (95% CI: 0.56, 1.01) in patients with a TPS < 1%. The OS HR was 0.55 (95% CI: 0.33, 0.92) in patients with a TPS ≥ 50%, 0.69 (95% CI: 0.44, 1.07) in patients with a TPS = 1 - 49% and 0.91 (95% CI: 0.63, 1.32) in patients with a TPS < 1%.

KEYNOTE-091: Placebo-controlled study for the adjuvant treatment of patients with resected NSCLC
The efficacy of pembrolizumab was investigated in KEYNOTE-091, a multicentre, randomised, triple-blind, placebo-controlled study in patients with NSCLC who are at high risk (stage IB [T2a ≥ 4 cm], II or IIIA by AJCC 7th edition) of recurrence following complete resection, regardless of tumour PD-L1 expression status, no prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy, and no prior or planned adjuvant radiotherapy for the current malignancy. Testing for genomic tumour aberrations/oncogenic drivers was not mandatory for enrolment.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage IB [T2a ≥ 4 cm], II or IIIA according to the 7th edition staging system: Tumour size ≥ 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade

the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary. The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients may or may not have received adjuvant chemotherapy as recommended by their physician. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 4 cycles of adjuvant chemotherapy were ineligible. Randomisation was stratified by stage (IB vs. II vs. IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs. adjuvant chemotherapy), PD-L1 status (TPS < 1% [negative] vs. TPS 1-49% vs. TPS ≥ 50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomised (1:1) to receive pembrolizumab 200 mg (n=590) or placebo (n=587) intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately 1 year (18 doses). Patients underwent imaging every 12 weeks after the first dose of pembrolizumab for the first year, then every 6 months for years 2 to 3, and then annually up to the end of year 5. After year 5, imaging is performed as per local standard of care.

Of 1 177 patients randomised, 1 010 (86%) received adjuvant platinum-based chemotherapy following complete resection. Among these 1 010 patients in KEYNOTE-091, baseline characteristics were: median age of 64 years (range: 35 to 84), 49% age 65 or older; 68% male; and 77% White, 18% Asian, 86% current or former smokers. Sixty-one percent and 39% had ECOG performance of 0 or 1, respectively. Twelve percent had stage IB (T2a ≥ 4 cm), 57% had stage II, and 31% had stage IIIA disease. Thirty-nine percent had tumour PD-L1 expression TPS < 1% [negative], 33% had TPS 1-49%, 28% had TPS ≥ 50%. Seven percent had known EGFR mutations, thirty-eight percent without EGFR mutations and in fifty-six percent EGFR mutation status was unknown. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The primary efficacy outcome measures were investigator-assessed disease-free survival (DFS) in the overall population and in the population with tumour PD-L1 expression TPS ≥ 50% where DFS was defined as the time between the date of randomisation and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death, whichever occurred first. Secondary efficacy outcome measures were investigator-assessed DFS in the population with tumour PD-L1 expression TPS ≥ 1%, and OS in the overall population and in the populations with tumour PD-L1 expression TPS ≥ 50% and TPS ≥ 1%.

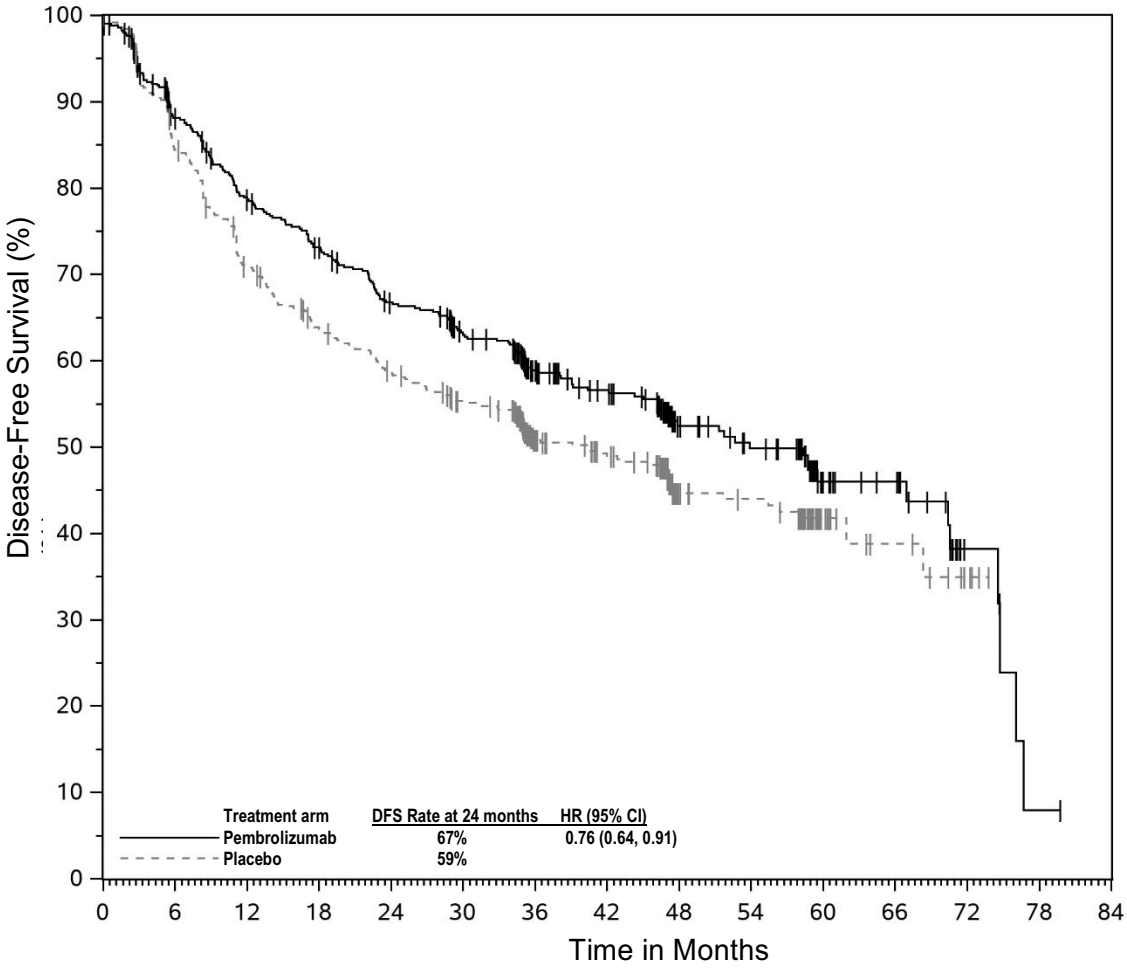
The study demonstrated a statistically significant improvement in DFS in the overall population (HR = 0.76 [95% CI: 0.63, 0.91; p = 0.0014]) at a pre-specified interim analysis with a median follow-up time of 32.4 months (range: 0.6 to 68 months) for patients randomised to the pembrolizumab arm compared to patients randomised to the placebo arm. Table 13 and Figure 10 summarise efficacy results in patients who received adjuvant chemotherapy at the final analysis for DFS performed at a median follow-up time of 46.7 months (range: 0.6 to 84.2). At the time of this analysis, OS results were not mature with only 58% of pre-specified OS events in the overall population. An exploratory analysis of OS suggested a trend in favour of pembrolizumab compared to placebo with a HR of 0.79 (95% CI: 0.62, 1.01) in patients who received adjuvant chemotherapy.

Table 13: Efficacy results in KEYNOTE-091 for patients who received adjuvant chemotherapy

Endpoint	Pembrolizumab 200 mg every 3 weeks n=506	Placebo n=504
DFS		
Number (%) of patients with event	225 (44%)	262 (52%)
Hazard ratio* (95% CI)	0.76 (0.64, 0.91)	
Median in months (95% CI)	53.8 (46.2, 70.4)	40.5 (32.9, 47.4)

* Based on the multivariate Cox regression model

Figure 10: Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-091 (for patients who received adjuvant chemotherapy)



Number at Risk

Pembrolizumab	506	422	373	344	309	281	190	166	85	74	31	23	6	1	0
Placebo	504	422	351	309	284	258	169	151	67	61	19	11	4	0	0

KEYNOTE-024: Controlled study of NSCLC patients naïve to treatment

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-024, a multicentre, open-label, controlled study for the treatment of previously untreated metastatic NSCLC. Patients had PD-L1 expression with a ≥ 50% TPS based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients were randomised (1:1) to receive pembrolizumab at a dose of 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin,

pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance.). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with EGFR or ALK genomic tumour aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Assessment of tumour status was performed every 9 weeks. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive pembrolizumab.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White, 15% Asian; and ECOG performance status 0 and 1 in 35% and 65%, respectively. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 14 summarises key efficacy measures for the entire intent to treat (ITT) population. PFS and ORR results are reported from an interim analysis at a median follow-up of 11 months. OS results are reported from the final analysis at a median follow-up of 25 months.

Table 14: Efficacy results in KEYNOTE-024

Endpoint	Pembrolizumab 200 mg every 3 weeks n=154	Chemotherapy n=151
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value†	< 0.001	
Median in months (95% CI)	10.3 (6.7, NA)	6.0 (4.2, 6.2)
OS		
Number (%) of patients with event	73 (47%)	96 (64%)
Hazard ratio* (95% CI)	0.63 (0.47, 0.86)	
p-Value†	0.002	
Median in months (95% CI)	30.0 (18.3, NA)	14.2 (9.8, 19.0)
Objective response rate		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response	4%	1%
Partial response	41%	27%
Response duration‡		
Median in months (range)	Not reached (1.9+, 14.5+)	6.3 (2.1+, 12.6+)
% with duration ≥ 6 months	88%§	59%¶

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best objective response as confirmed complete or partial response

§ Based on Kaplan-Meier estimates; includes 43 patients with responses of 6 months or longer

¶ Based on Kaplan-Meier estimates; includes 16 patients with responses of 6 months or longer

NA = not available

Figure 11: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-024 (intent to treat population)

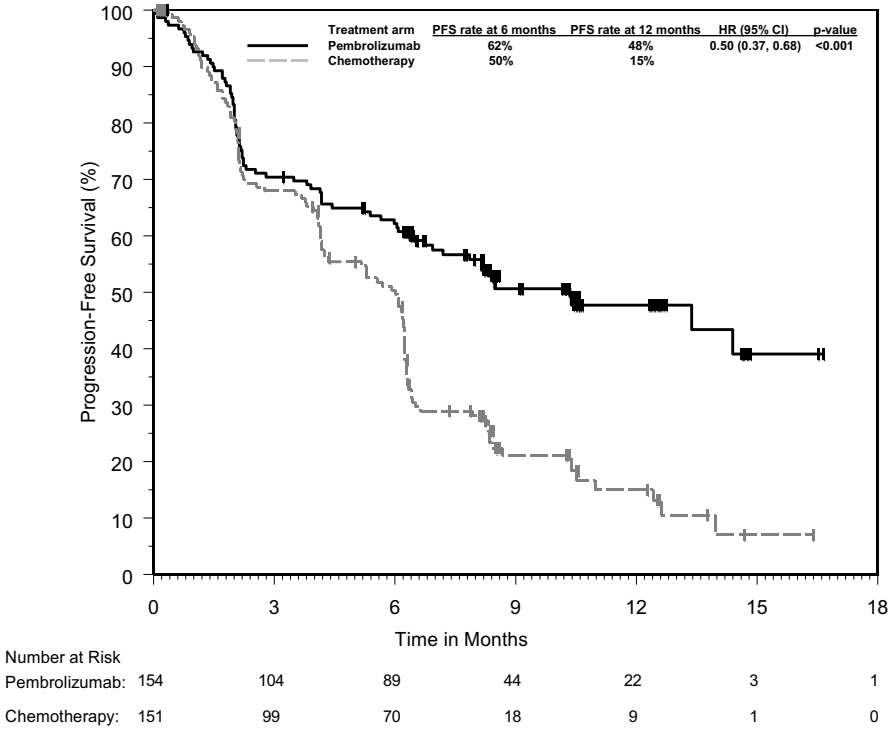
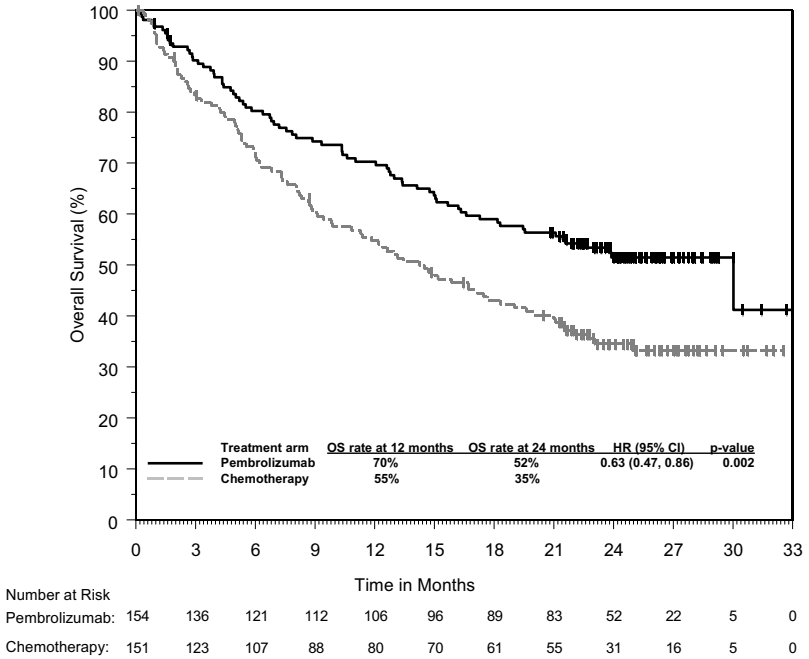


Figure 12: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



In a subgroup analysis, a reduced survival benefit of pembrolizumab compared to chemotherapy was observed in the small number of patients who were never-smokers; however, due to the small number of patients, no definitive conclusions can be drawn from these data.

KEYNOTE-042: Controlled study of NSCLC patients naïve to treatment

The safety and efficacy of pembrolizumab were also investigated in KEYNOTE-042, a multicentre, controlled study for the treatment of previously untreated locally advanced or metastatic NSCLC. The

study design was similar to that of KEYNOTE-024, except that patients had PD-L1 expression with a ≥ 1% TPS based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients were randomised (1:1) to receive pembrolizumab at a dose of 200 mg every 3 weeks (n=637) or investigator's choice platinum-containing chemotherapy (n=637; including pemetrexed+carboplatin or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance.). Assessment of tumour status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

Among the 1 274 patients in KEYNOTE-042, 599 (47%) had tumours that expressed PD-L1 with TPS ≥ 50% based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 599 patients included: median age 63 years (45% age 65 or older); 69% male; 63% White and 32% Asian; 17% Hispanic or Latino; and ECOG performance status 0 and 1 in 31% and 69%, respectively. Disease characteristics were squamous (37%) and non-squamous (63%); stage IIIA (0.8%); stage IIIB (9%); stage IV (90%); and treated brain metastases (6%).

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR (as assessed by BICR using RECIST 1.1). The study demonstrated a statistically significant improvement in OS for patients whose tumours expressed PD-L1 TPS ≥ 1% randomised to pembrolizumab monotherapy compared to chemotherapy (HR 0.82; 95% CI 0.71, 0.93 at the final analysis) and in patients whose tumours expressed PD-L1 TPS ≥ 50% randomised to pembrolizumab monotherapy compared to chemotherapy. Table 15 summarises key efficacy measures for the TPS ≥ 50% population at the final analysis performed at a median follow-up of 15.4 months. The Kaplan-Meier curve for OS for the TPS ≥ 50% population based on the final analysis is shown in Figure 13.

Table 15: Efficacy results (PD-L1 TPS ≥ 50%) in KEYNOTE-042

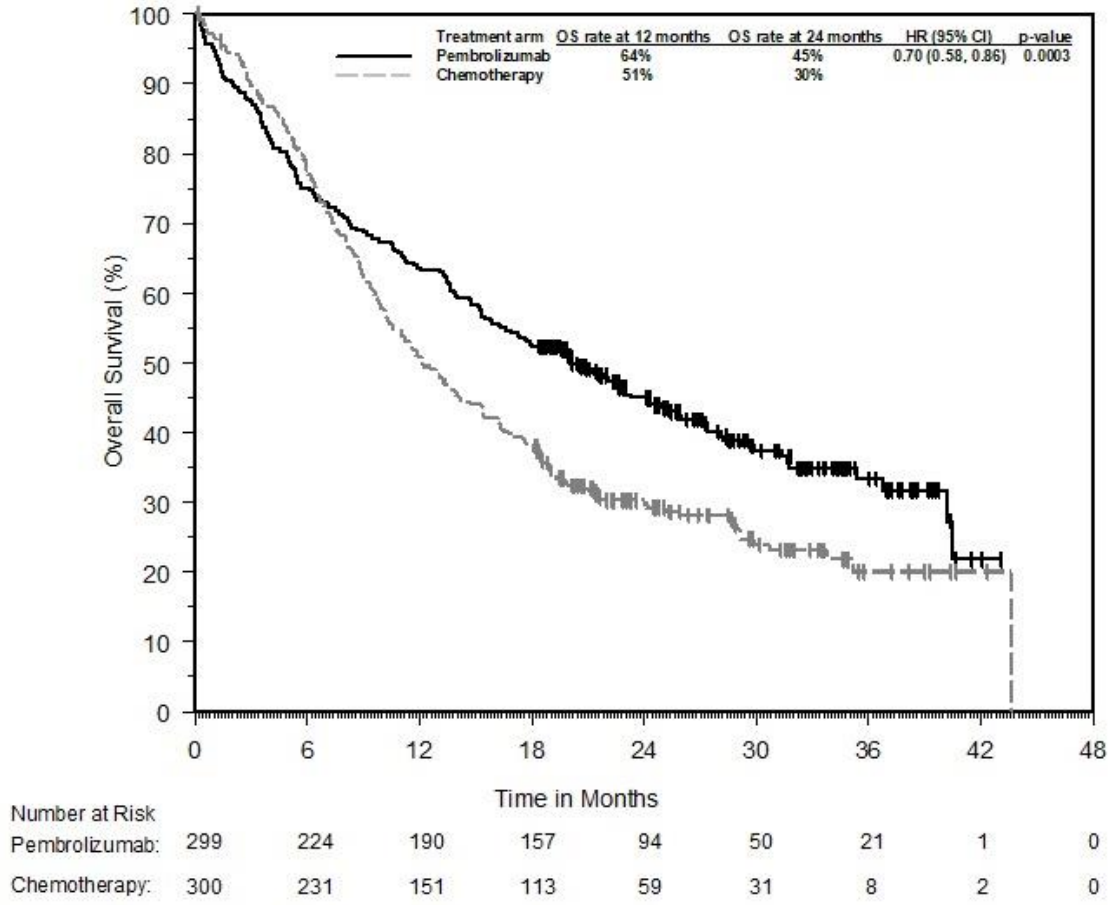
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS		
Number (%) of patients with event	180 (60%)	220 (73%)
Hazard ratio* (95% CI)	0.70 (0.58, 0.86)	
p-Value†	0.0003	
Median in months (95% CI)	20.0 (15.9, 24.2)	12.2 (10.4, 14.6)
PFS		
Number (%) of patients with event	238 (80%)	250 (83%)
Hazard ratio* (95% CI)	0.84 (0.70, 1.01)	
Median in months (95% CI)	6.5 (5.9, 8.5)	6.4 (6.2, 7.2)
Objective response rate		
ORR % (95% CI)	39% (34, 45)	32% (27, 38)
Complete response	1%	0.3%
Partial response	38%	32%
Response duration‡		
Median in months (range)	22.0 (2.1+, 36.5+)	10.8 (1.8+, 30.4+)
% with duration ≥ 18 months	57%	34%

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best objective response as confirmed complete or partial response

Figure 13: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-042 (patients with PD-L1 expression TPS ≥ 50%, intent to treat population)



The results of a post-hoc exploratory subgroup analysis indicated a trend towards reduced survival benefit of pembrolizumab compared to chemotherapy, during both the first 4 months and throughout the entire duration of treatment, in patients who were never-smokers. However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

KEYNOTE-189: Controlled study of combination therapy in non-squamous NSCLC patients naïve to treatment

The efficacy of pembrolizumab in combination with pemetrexed and platinum chemotherapy was investigated in a multicentre, randomised, active-controlled, double-blind study, KEYNOTE-189. Key eligibility criteria were metastatic non-squamous NSCLC, no prior systemic treatment for metastatic NSCLC, and no EGFR or ALK genomic tumour aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomised (2:1) to receive one of the following regimens:

- Pembrolizumab 200 mg with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by pembrolizumab 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks (n=410)
- Placebo with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 intravenously every 3 weeks (n=206)

Treatment with pembrolizumab continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving clinical benefit as

determined by the investigator. For patients who completed 24 months of therapy or had a complete response, treatment with pembrolizumab could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of tumour status was performed at Week 6 and Week 12, followed by every 9 weeks thereafter. Patients receiving placebo plus chemotherapy who experienced independently-verified progression of disease were offered pembrolizumab as monotherapy.

Among the 616 patients in KEYNOTE-189, baseline characteristics were: median age of 64 years (49% age 65 or older); 59% male; 94% White and 3% Asian; 43% and 56% ECOG performance status of 0 or 1 respectively; 31% PD-L1 negative (TPS < 1%); and 18% with treated or untreated brain metastases at baseline.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. Table 16 summarises key efficacy measures and Figures 14 and 15 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 18.8 months.

Table 16: Efficacy results in KEYNOTE-189

Endpoint	**Pembrolizumab + Pemetrexed + Platinum Chemotherapy n=410**	**Placebo + Pemetrexed + Platinum Chemotherapy n=206**
OS[*]		
Number (%) of patients with event	258 (63%)	163 (79%)
Hazard ratio[†] (95% CI)	0.56 (0.46, 0.69)	
p-Value[‡]	< 0.00001	
Median in months (95% CI)	22.0 (19.5, 24.5)	10.6 (8.7, 13.6)
PFS		
Number (%) of patients with event	337 (82%)	197 (96%)
Hazard ratio[†] (95% CI)	0.49 (0.41, 0.59)	
p-Value[‡]	< 0.00001	
Median in months (95% CI)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)
Objective response rate		
ORR[§] % (95% CI)	48% (43, 53)	20% (15, 26)
Complete response	1.2%	0.5%
Partial response	47%	19%
p-Value[¶]	< 0.0001	
Response duration		
Median in months (range)	12.5 (1.1+, 34.9+)	7.1 (2.4, 27.8+)
% with duration ≥ 12 months[#]	53%	27%

[*] A total of 113 patients (57%) who discontinued study treatment in the placebo plus chemotherapy arm crossed over to receive monotherapy pembrolizumab or received a checkpoint inhibitor as subsequent therapy

[†] Based on the stratified Cox proportional hazard model

[‡] Based on stratified log-rank test

[§] Based on patients with a best objective response as confirmed complete or partial response

[¶] Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status

[#] Based on Kaplan-Meier estimation

Figure 14: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

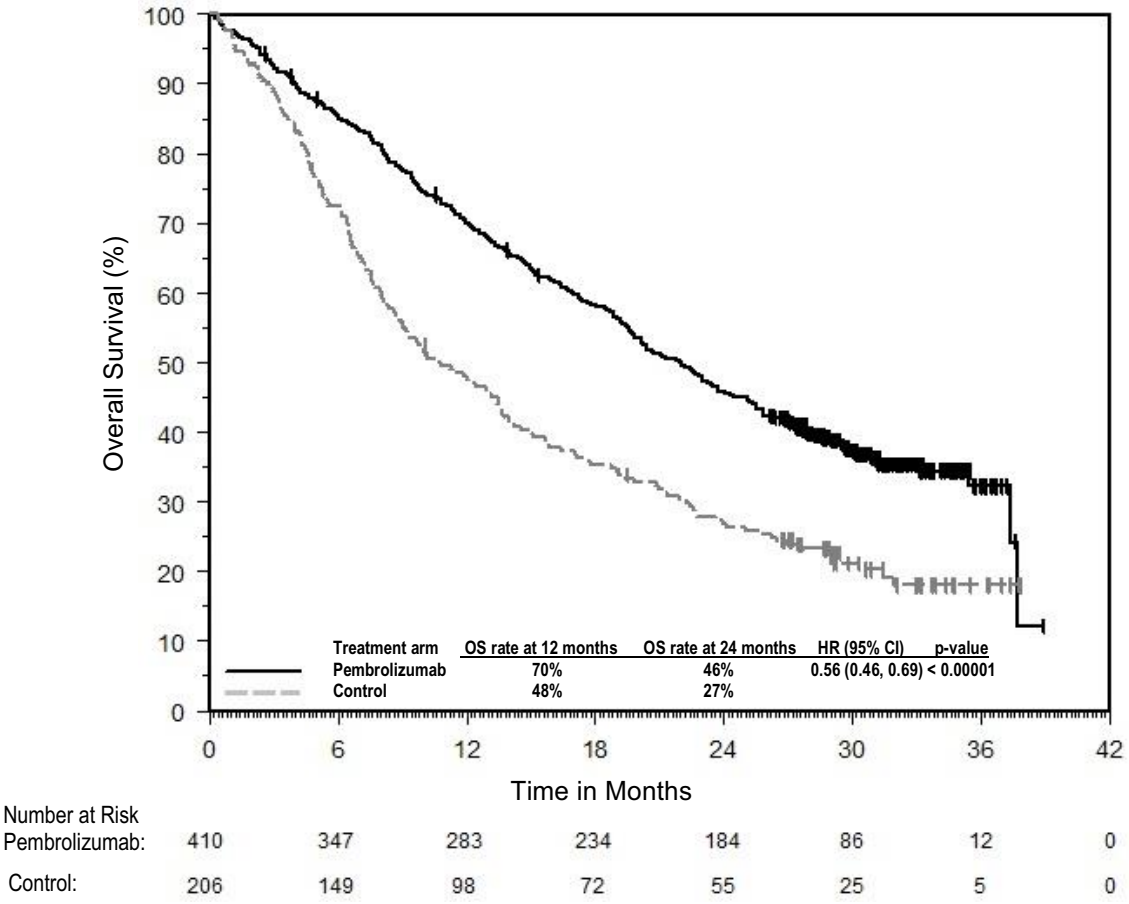
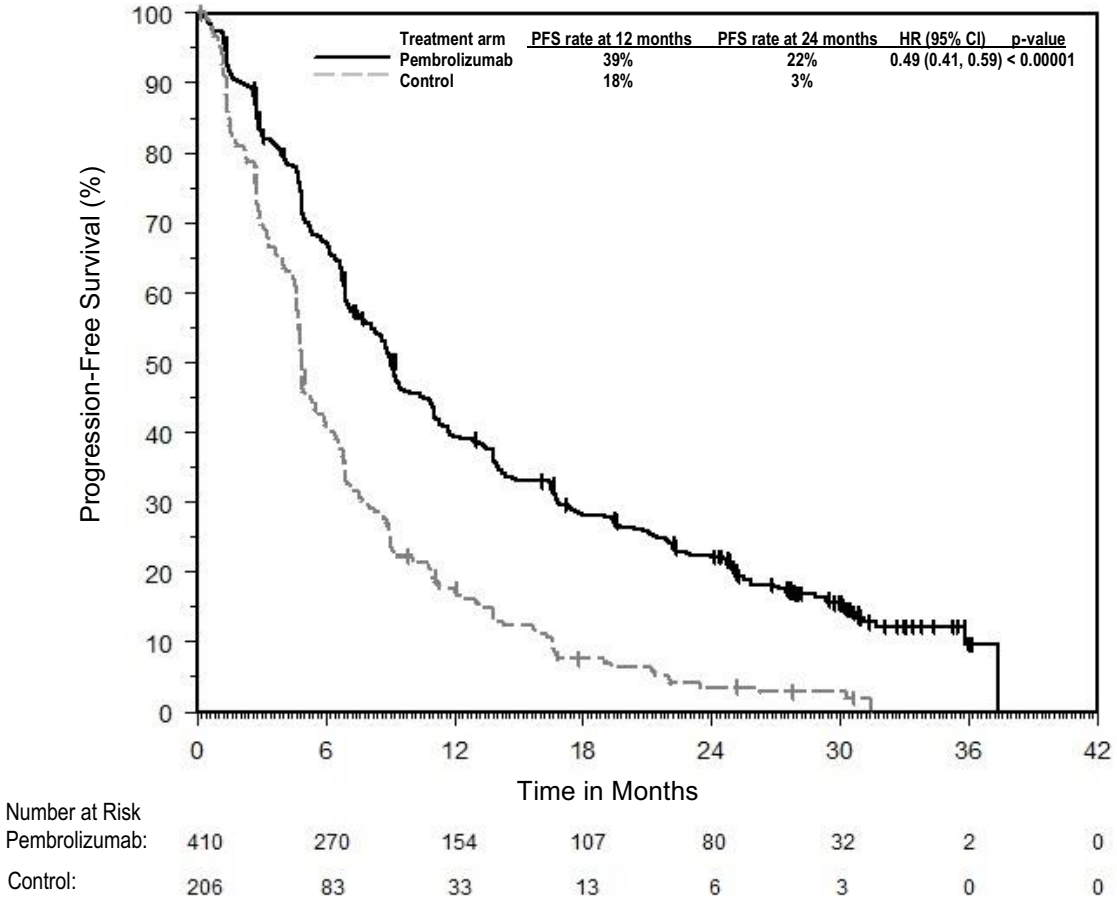


Figure 15: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



An analysis was performed in KEYNOTE-189 in patients who had PD-L1 TPS < 1% [pembrolizumab combination: n=127 (31%) vs. chemotherapy: n=63 (31%)], TPS 1-49% [pembrolizumab combination: n=128 (31%) vs. chemotherapy: n=58 (28%)] or ≥ 50% [pembrolizumab combination: n=132 (32%) vs. chemotherapy: n=70 (34%)] (see Table 17).

Table 17: Efficacy results by PD-L1 expression in KEYNOTE-189*

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1%		**TPS 1 to 49%**		**TPS ≥ 50%**	
OS Hazard ratio† (95% CI)	0.51 (0.36, 0.71)		0.66 (0.46, 0.96)		0.59 (0.40, 0.86)	
PFS Hazard ratio† (95% CI)	0.67 (0.49, 0.93)		0.53 (0.38, 0.74)		0.35 (0.25, 0.49)	
ORR %	33%	14%	50%	21%	62%	26%

* Based on final analysis

† Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model

At final analysis, a total of 57 NSCLC patients aged ≥ 75 years were enrolled in study KEYNOTE-189 (35 in the pembrolizumab combination and 22 in the control). A HR=1.54 [95% CI 0.76, 3.14] in OS and HR=1.12 [95% CI 0.56, 2.22] in PFS for pembrolizumab combination vs. chemotherapy was reported within this study subgroup. Data about efficacy of pembrolizumab in combination with platinum chemotherapy are limited in this patient population.

KEYNOTE-407: Controlled study of combination therapy in squamous NSCLC patients naïve to treatment

The efficacy of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumour PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomisation was stratified by tumour PD-L1 expression (TPS < 1% [negative] vs. TPS ≥ 1%), investigator's choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomised (1:1) to one of the following treatment arms via intravenous infusion:

- Pembrolizumab 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by pembrolizumab 200 mg every 3 weeks. Pembrolizumab was administered prior to chemotherapy on Day 1.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with pembrolizumab or placebo continued until RECIST 1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients in the placebo arm were offered pembrolizumab as a single agent at the time of disease progression.

Assessment of tumour status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter.

A total of 559 patients were randomised. The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; ECOG performance status of 0 (29%) and 1 (71%); and 8% with treated brain metastases at baseline. Thirty-five percent had tumour PD-L1 expression TPS < 1% [negative]; 19% were East Asian; and 60% received paclitaxel.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. Table 18 summarises key efficacy measures and Figures 16 and 17 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 14.3 months.

Table 18: Efficacy results in KEYNOTE-407

Endpoint	Pembrolizumab Carboplatin Paclitaxel/Nab-paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-paclitaxel n=281
OS[*]		
Number (%) of patients with event	168 (60%)	197 (70%)
Median in months (95% CI)	17.1 (14.4, 19.9)	11.6 (10.1, 13.7)
Hazard ratio[†] (95% CI)	0.71 (0.58, 0.88)	
p-Value[‡]	0.0006	
PFS		
Number (%) of patients with event	217 (78%)	252 (90%)
Median in months (95% CI)	8.0 (6.3, 8.4)	5.1 (4.3, 6.0)
Hazard ratio[†] (95% CI)	0.57 (0.47, 0.69)	
p-Value[‡]	< 0.0001	
Objective response rate		
ORR % (95% CI)	63% (57, 68)	38% (33, 44)
Complete response	2.2%	3.2%
Partial response	60%	35%
p-Value[§]	< 0.0001	
Response duration		
Median in months (range)	8.8 (1.3+, 28.4+)	4.9 (1.3+, 28.3+)
% with duration ≥ 12 months[¶]	38%	25%

[*] A total of 138 patients (51%) who discontinued study treatment in the placebo plus chemotherapy arm crossed over to receive monotherapy pembrolizumab or received a checkpoint inhibitor as subsequent therapy

[†] Based on the stratified Cox proportional hazard model

[‡] Based on stratified log-rank test

[§] Based on method by Miettinen and Nurminen

[¶] Based on Kaplan-Meier estimation

Figure 16: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

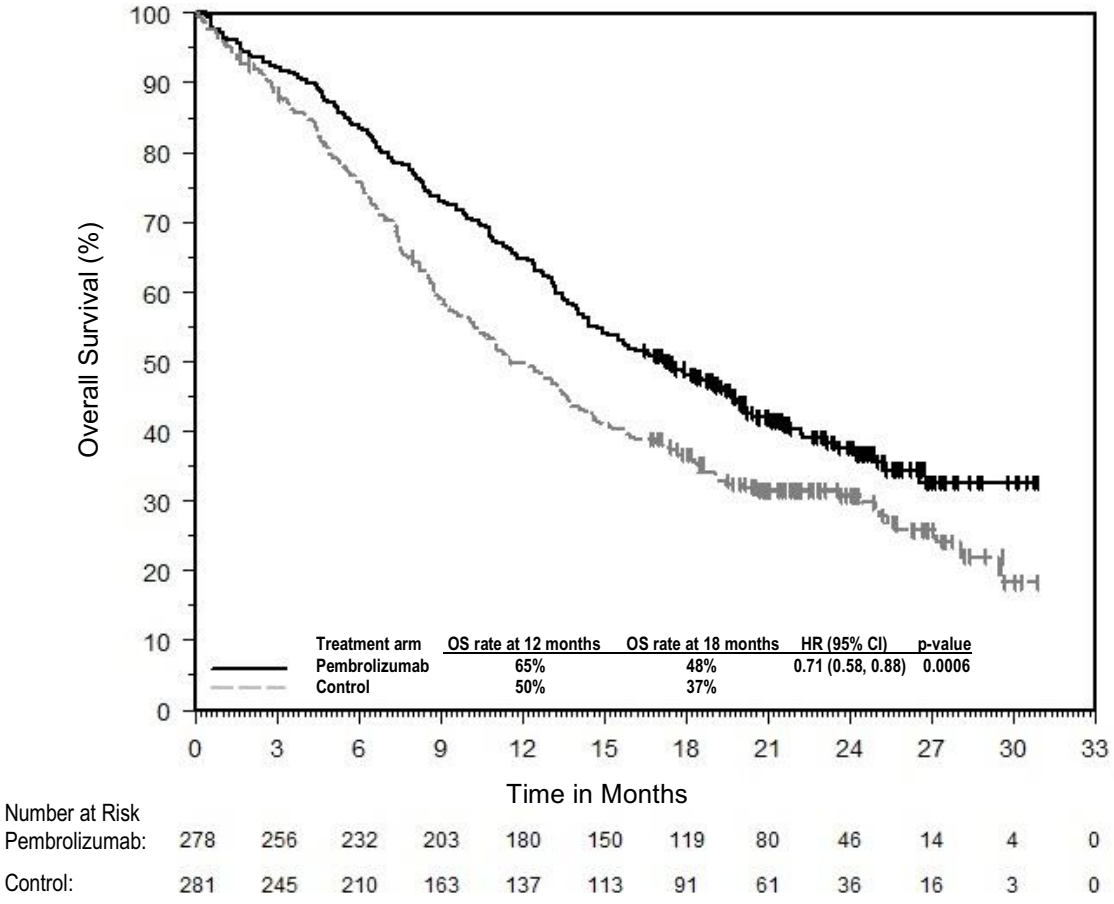
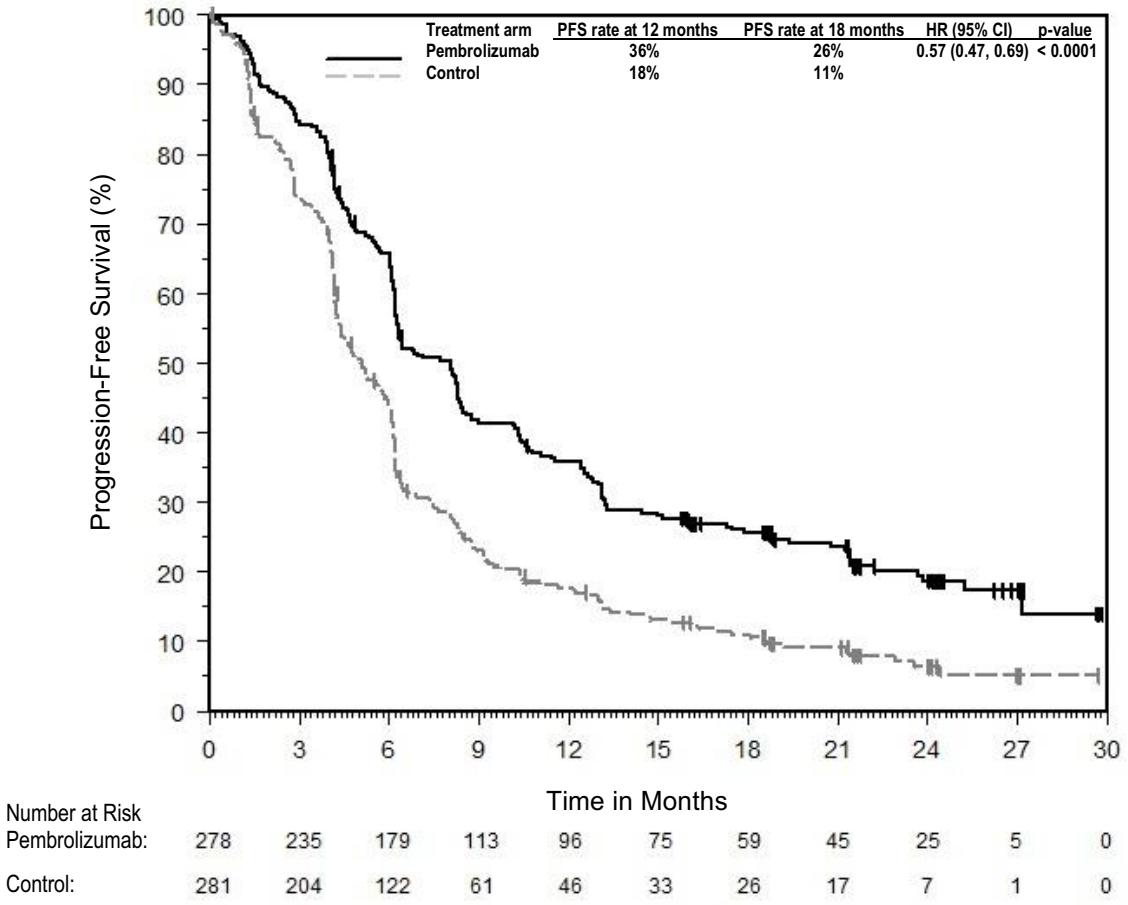


Figure 17: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



An analysis was performed in KEYNOTE-407 in patients who had PD-L1 TPS < 1% [pembrolizumab plus chemotherapy arm: n=95 (34%) vs. placebo plus chemotherapy arm: n=99 (35%)], TPS 1% to 49% [pembrolizumab plus chemotherapy arm: n=103 (37%) vs. placebo plus chemotherapy arm: n=104 (37%)] or TPS ≥ 50% [pembrolizumab plus chemotherapy arm: n=73 (26%) vs. placebo plus chemotherapy arm: n=73 (26%)] (see Table 19).

Table 19: Efficacy results by PD-L1 expression in KEYNOTE-407*

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1%		TPS 1 to 49%		TPS ≥ 50%	
OS Hazard ratio† (95% CI)	0.79 (0.56, 1.11)		0.59 (0.42, 0.84)		0.79 (0.52, 1.21)	
PFS Hazard ratio† (95% CI)	0.67 (0.49, 0.91)		0.52 (0.38, 0.71)		0.43 (0.29, 0.63)	
ORR %	67%	41%	55%	42%	64%	30%

* Based on final analysis

† Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model

At final analysis, a total of 65 NSCLC patients aged ≥ 75 years were enrolled in study KEYNOTE-407 (34 in the pembrolizumab combination and 31 in the control). An HR=0.81 [95% CI 0.43, 1.55] in OS, an HR=0.61 [95% CI 0.34, 1.09] in PFS, and an ORR of 62% and 45% for pembrolizumab combination vs. chemotherapy was reported within this study subgroup. Data about efficacy of pembrolizumab in combination with platinum chemotherapy are limited in this patient population.

KEYNOTE-010: Controlled study of NSCLC patients previously treated with chemotherapy

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-010, a multicentre, open-label, controlled study for the treatment of advanced NSCLC in patients previously treated with platinum-containing chemotherapy. Patients had PD-L1 expression with a ≥ 1% TPS based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients with EGFR activation mutation or ALK translocation also had disease progression on approved therapy for these mutations prior to receiving pembrolizumab. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=344) or 10 mg/kg bw (n=346) every 3 weeks or docetaxel at a dose of 75 mg/m^2 every 3 weeks (n=343) until disease progression or unacceptable toxicity. The study excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Assessment of tumour status was performed every 9 weeks.

The baseline characteristics for this population included: median age 63 years (42% age 65 or older); 61% male; 72% White and 21% Asian and 34% and 66% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (70%); stage IIIA (2%); stage IIIB (7%); stage IV (91%); stable brain metastases (15%) and the incidence of mutations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%) or two or more (29%) treatment lines.

The primary efficacy outcome measures were OS and PFS as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 20 summarises key efficacy measures for the entire population (TPS ≥ 1%) and for the-patients with TPS ≥ 50%, and Figure 18 shows the Kaplan-Meier curve for OS (TPS ≥ 1%), based on a final analysis with median follow-up of 42.6 months.

Table 20: Response to pembrolizumab 2 or 10 mg/kg bw every 3 weeks in previously treated patients with NSCLC in KEYNOTE-010

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks	Pembrolizumab 10 mg/kg bw every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥ 1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	284 (83%)	264 (76%)	295 (86%)
Hazard ratio* (95% CI)	0.77 (0.66, 0.91)	0.61 (0.52, 0.73)	---
p-Value†	0.00128	< 0.001	---
Median in months (95% CI)	10.4 (9.5, 11.9)	13.2 (11.2, 16.7)	8.4 (7.6, 9.5)
PFS‡			
Number (%) of patients with event	305 (89%)	292 (84%)	314 (92%)
Hazard ratio* (95% CI)	0.88 (0.75, 1.04)	0.75 (0.63, 0.89)	---
p-Value†	0.065	< 0.001	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.7, 4.5)	4.1 (3.8, 4.5)
Objective response rate‡			
ORR % (95% CI)	20% (16, 25)	21% (17, 26)	9% (6, 13)
Complete response	2%	3%	0%
Partial response	18%	18%	9%
Response duration‡,§			
Median in months (range)	Not reached (2.8, 46.2+)	37.8 (2.0+, 49.3+)	7.1 (1.4+, 16.8)
% ongoing¶	42%	43%	6%
TPS ≥ 50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	97 (70%)	102 (68%)	127 (84%)
Hazard ratio* (95% CI)	0.56 (0.43, 0.74)	0.50 (0.38, 0.65)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	15.8 (10.8, 22.5)	18.7 (12.1, 25.3)	8.2 (6.4, 9.8)
PFS‡			
Number (%) of patients with event	107 (77%)	115 (76%)	138 (91%)
Hazard ratio* (95% CI)	0.59 (0.45, 0.77)	0.53 (0.41, 0.70)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	5.3 (4.1, 7.9)	5.2 (4.1, 8.1)	4.2 (3.8, 4.7)
Objective response rate‡			
ORR % (95% CI)	32% (24, 40)	32% (25, 41)	9% (5, 14)
Complete response	4%	4%	0%
Partial response	27%	28%	9%
Response duration‡,§			
Median in months (range)	Not reached (2.8, 44.0+)	37.5 (2.0+, 49.3+)	8.1 (2.6, 16.8)
% ongoing¶	55%	47%	8%

* Hazard ratio (pembrolizumab compared to docetaxel) based on the stratified Cox proportional hazard model

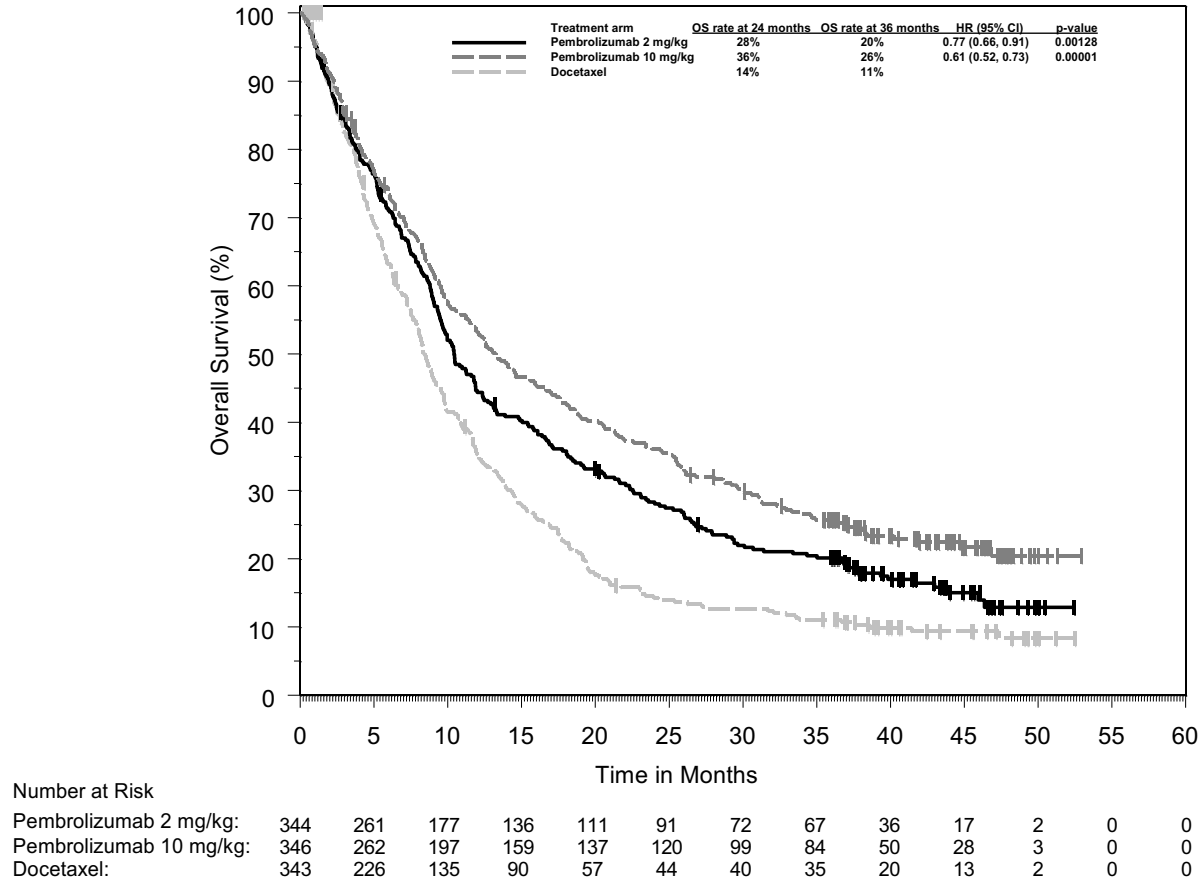
† Based on stratified log-rank test

‡ Assessed by BICR using RECIST 1.1

§ Based on patients with a best objective response as confirmed complete or partial response

¶ Ongoing response includes all responders who at the time of analysis were alive, progression-free, did not initiate new anti-cancer therapies and had not been determined to be lost to follow-up

Figure 18: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-010 (patients with PD-L1 expression TPS ≥ 1%, intent to treat population)



Efficacy results were similar for the 2 mg/kg bw and 10 mg/kg bw pembrolizumab arms. Efficacy results for OS were consistent regardless of the age of tumour specimen (new vs. archival) based on an intergroup comparison.

In subgroup analyses, a reduced survival benefit of pembrolizumab compared to docetaxel was observed for patients who were never-smokers or patients with tumours harbouring EGFR activating mutations who received at least platinum-based chemotherapy and a tyrosine kinase inhibitor; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 have not been established.

Classical Hodgkin lymphoma
KEYNOTE-204: Controlled study in patients with relapsed or refractory classical Hodgkin lymphoma (cHL)
The efficacy of pembrolizumab was investigated in KEYNOTE-204, a randomised, open-label, active-controlled study conducted in 304 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or > 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the study. Randomisation was stratified by prior ASCT (yes vs. no) and disease status after frontline therapy (primary refractory vs. relapse less than 12 months after completion vs. relapse 12 months or more after completion). Patients were randomised (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg intravenously every 3 weeks
- Brentuximab vedotin (BV) 1.8 mg/kg bw intravenously every 3 weeks.

Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or a maximum of 35 cycles. Limited data are currently available on response duration following pembrolizumab discontinuation at cycle 35. Response was assessed every 12 weeks, with the first planned post-baseline assessment at Week 12.

Among the 304 patients in KEYNOTE-204, there is a subpopulation consisting of 112 patients who failed a transplant before enrolling and 137 who failed 2 or more prior therapies and were ineligible for ASCT at the time of enrolment. The baseline characteristics of these 249 patients were: median age 34 years (11% age 65 or older); 56% male; 80% White and 7% Asian and 58% and 41% with an ECOG performance status 0 and 1, respectively. Approximately 30% were refractory to frontline chemotherapy and ~ 45% had received prior ASCT. Nodular-sclerosis was the more represented cHL histological subtype (~ 81%) and bulky disease, B symptoms and bone marrow involvement were present in approximately 21%, 28% and 4% of patients, respectively.

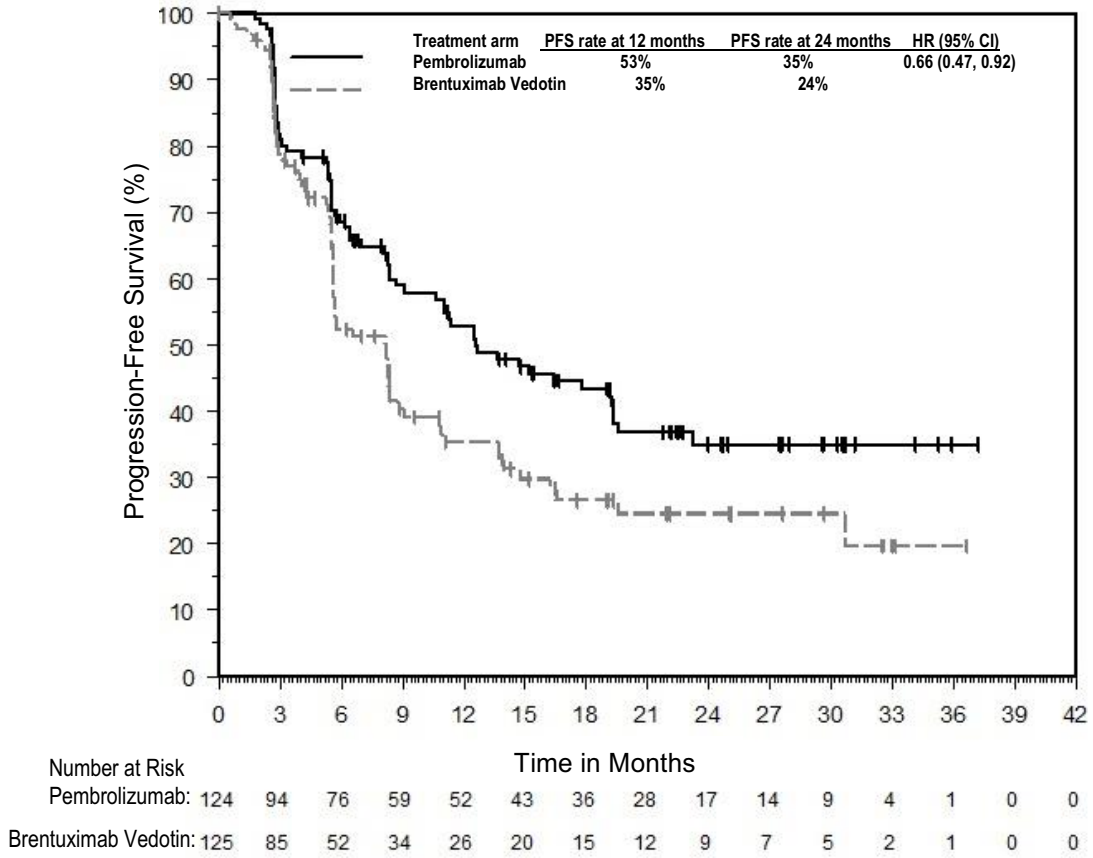
The primary efficacy outcome was PFS and the secondary efficacy outcome measure was ORR, both assessed by BICR according to the 2007 revised International Working Group (IWG) criteria. The additional primary efficacy outcome measure, OS, was not formally assessed at the time of the analysis. In the ITT population, the median follow-up time for 151 patients treated with pembrolizumab was 24.9 months (range: 1.8 to 42.0 months). The initial analysis resulted in a HR for PFS of 0.65 (95% CI: 0.48, 0.88) with a one-sided p value of 0.0027. The ORR was 66% for pembrolizumab compared to 54% for standard treatment with a p-Value of 0.0225. Table 21 summarises the efficacy results in the subpopulation. Efficacy results in this subpopulation were consistent with the ITT population. The Kaplan-Meier curve for PFS for this subpopulation is shown in Figure 19.

Table 21: Efficacy results in cHL patients who failed a transplant before enrolling or who failed 2 or more prior therapies and were ineligible for ASCT in KEYNOTE-204

Endpoint	**Pembrolizumab** **200 mg every 3 weeks n=124**	**Brentuximab vedotin 1.8 mg/kg bw every 3 weeks n=125**
PFS		
Number (%) of patients with event	68 (55%)	75 (60%)
Hazard ratio* (95% CI)	0.66 (0.47, 0.92)	
Median in months (95% CI)	12.6 (8.7, 19.4)	8.2 (5.6, 8.8)
Objective response rate		
ORR‡ % (95% CI)	65% (56.3, 73.6)	54% (45.3, 63.3)
Complete response	27%	22%
Partial response	39%	33%
Stable disease	12%	23%
Response duration		
Median in months (range)	20.5 (0.0+, 33.2+)	11.2 (0.0+, 33.9+)
Number (%¶) of patients with duration ≥ 6 months	53 (80.8%)	28 (61.2%)
Number (%¶) of patients with duration ≥ 12 months	37 (61.7%)	17 (49.0%)

* Based on the stratified Cox proportional hazard model
‡ Based on patients with a best overall response as complete or partial response
¶ Based on Kaplan-Meier estimation

Figure 19: Kaplan-Meier curve for progression-free survival by treatment arm in cHL patients who failed a transplant before enrolling or who failed 2 or more prior therapies and were ineligible for ASCT in KEYNOTE-204



KEYNOTE-087 and KEYNOTE-013: Open-label studies in patients with relapsed or refractory cHL

The efficacy of pembrolizumab was investigated in KEYNOTE-087 and KEYNOTE-013, two multicentre, open-label studies for the treatment of 241 patients with cHL. These studies enrolled patients who failed ASCT and BV, who were ineligible for ASCT because they were unable to achieve a complete or partial remission to salvage chemotherapy and failed BV, or who failed ASCT and did not receive BV. Five study subjects were ineligible to ASCT due to reasons other than failure to salvage chemotherapy. Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic transplant within the past 5 years (or > 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either study. Patients received pembrolizumab 200 mg every 3 weeks (n=210; KEYNOTE-087) or 10 mg/kg bw every 2 weeks (n=31; KEYNOTE-013) until unacceptable toxicity or documented disease progression.

Among KEYNOTE-087 patients, the baseline characteristics were median age 35 years (9% age 65 or older); 54% male; 88% White; and 49% and 51% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range: 1 to 12). Eighty-one percent were refractory to at least one prior therapy, including 34% who were refractory to first-line therapy. Sixty-one percent of patients had received ASCT, 38% were transplant ineligible; 17% had no prior brentuximab vedotin use; and 37% of patients had prior radiation therapy. Disease subtypes were 81% nodular sclerosis, 11% mixed cellularity, 4% lymphocyte-rich and 2% lymphocyte-depleted.

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (7% age 65 or older), 58% male, 94% White; and 45% and 55% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 5

(range: 2 to 15). Eighty-four percent were refractory to at least one prior therapy, including 35% who were refractory to first-line therapy. Seventy-four percent of patients had received ASCT, 26% were transplant ineligible, and 45% of patients had prior radiation therapy. Disease subtypes were 97% nodular sclerosis and 3% mixed cellularity.

The primary efficacy outcome measures (ORR and CRR) were assessed by BICR according to the IWG 2007 criteria. Secondary efficacy outcome measures were duration of response, PFS and OS. Response was assessed in KEYNOTE-087 and KEYNOTE-013 every 12 and 8 weeks, respectively, with the first planned post-baseline assessment at Week 12. Main efficacy results are summarised in Table 22.

Table 22: Efficacy results in KEYNOTE-087 and KEYNOTE-013

	KEYNOTE-087*	**KEYNOTE-013†**
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=210**	**Pembrolizumab 10 mg/kg bw every 2 weeks n=31**
Objective response rate‡		
ORR % (95% CI)	71% (64.8, 77.4)	58% (39.1, 75.5)
Complete remission	28%	19%
Partial remission	44%	39%
Response duration‡		
Median in months (range)	16.6 (0.0+, 62.1+)§	Not reached (0.0+, 45.6+)¶
% with duration ≥ 12-months	59%#	70%Þ
% with duration ≥ 24-months	45%ß	---
% with duration ≥ 60-months	25%à	---
Time to response		
Median in months (range)	2.8 (2.1, 16.5)§	2.8 (2.4, 8.6)¶
OS		
Number (%) of patients with event	59 (28%)	6 (19%)
12-month OS rate	96%	87%
24-month OS rate	91%	87%
60-month OS rate	71%	---

* Median follow-up time of 62.9 months
† Median follow-up time of 52.8 months
‡ Assessed by BICR according to the IWG 2007 criteria by PET CT scans
§ Based on patients (n=150) with a response by independent review
¶ Based on patients (n=18) with a response by independent review
# Based on Kaplan-Meier estimation; includes 62 patients with responses of 12 months or longer
Þ Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer
ß Based on Kaplan-Meier estimation; includes 37 patients with responses of 24 months or longer
à Based on Kaplan-Meier estimation; includes 4 patients with responses of 60 months or longer

Efficacy in elderly patients
Overall, 46 cHL patients ≥ 65 years were treated with pembrolizumab in studies KEYNOTE-087, KEYNOTE-013 and KEYNOTE-204. Data from these patients are too limited to draw any conclusion on efficacy in this population.

Urothelial carcinoma
KEYNOTE-045: Controlled study in urothelial carcinoma patients who have received prior platinum-containing chemotherapy
The safety and efficacy of pembrolizumab were evaluated in KEYNOTE-045, a multicentre, open-label, randomised (1:1), controlled study for the treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression on or after platinum-containing chemotherapy. Patients must have received first-line platinum-containing regimen for locally advanced/metastatic disease or as neoadjuvant/adjuvant treatment, with recurrence/progression ≤ 12 months following completion of therapy. Patients were randomised (1:1) to receive either

pembrolizumab 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune disease, a medical condition that required immunosuppression and patients with more than 2 prior lines of systemic chemotherapy for metastatic urothelial carcinoma. Patients with an ECOG performance status of 2 had to have a haemoglobin ≥ 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 3 months prior to enrolment. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among the 542 randomised patients in KEYNOTE-045, baseline characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 56% ECOG performance status of 1 and 1% ECOG performance status of 2; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumour in the lower tract and 14% had a primary tumour in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% was treated with other platinum-based regimens.

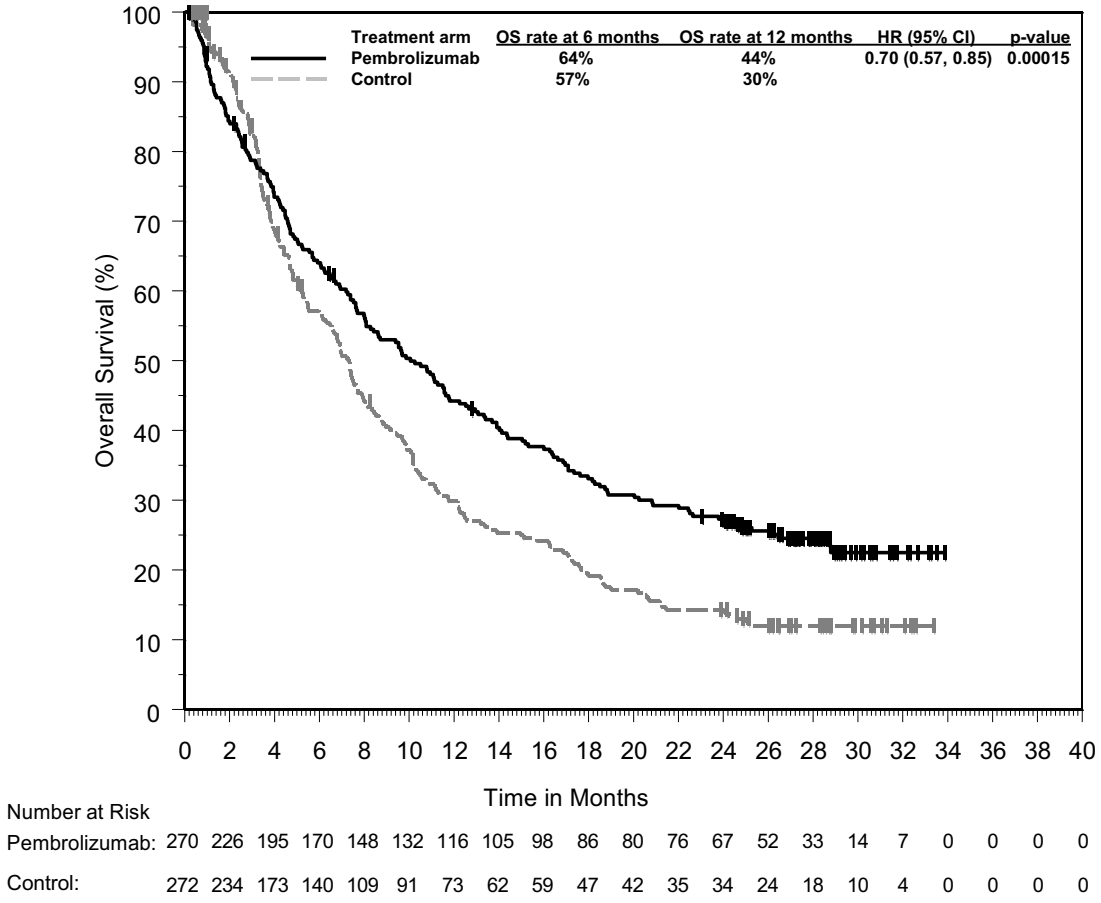
The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. Table 23 summarises the key efficacy measures for the ITT population at the final analysis. The Kaplan-Meier curve based on the final analysis for OS is shown in Figure 20. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to pembrolizumab as compared to chemotherapy. There was no statistically significant difference between pembrolizumab and chemotherapy with respect to PFS.

Table 23: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma previously treated with chemotherapy in KEYNOTE-045

Endpoint	Pembrolizumab 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	200 (74%)	219 (81%)
Hazard ratio[*] (95% CI)	0.70 (0.57, 0.85)	
p-Value[†]	< 0.001	
Median in months (95% CI)	10.1 (8.0, 12.3)	7.3 (6.1, 8.1)
PFS[‡]		
Number (%) of patients with event	233 (86%)	237 (87%)
Hazard ratio[*] (95% CI)	0.96 (0.79, 1.16)	
p-Value[†]	0.313	
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.4, 3.6)
Objective response rate[‡]		
ORR % (95% CI)	21% (16, 27)	11% (8, 15)
p-Value[§]	< 0.001	
Complete response	9%	3%
Partial response	12%	8%
Stable disease	17%	34%
Response duration[‡,¶]		
Median in months (range)	Not reached (1.6+, 30.0+)	4.4 (1.4+, 29.9+)
Number (%[#]) of patients with duration ≥ 6 months	46 (84%)	8 (47%)
Number (%[#]) of patients with duration ≥ 12 months	35 (68%)	5 (35%)

[*] Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model
[†] Based on stratified log-rank test
[‡] Assessed by BICR using RECIST 1.1
[§] Based on method by Miettinen and Nurminen
[¶] Based on patients with a best objective response as confirmed complete or partial response
[#] Based on Kaplan-Meier estimation

Figure 20: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-045 (intent to treat population)



An analysis was performed in KEYNOTE-045 in patients who had PD-L1 CPS < 10 [pembrolizumab: n=186 (69%) vs. chemotherapy: n=176 (65%)] or ≥ 10 [pembrolizumab: n=74 (27%) vs. chemotherapy: n=90 (33%)] in both pembrolizumab- and chemotherapy-treated arms (see Table 24).

Table 24: OS by PD-L1 expression

PD-L1 Expression	Pembrolizumab	Chemotherapy	
	OS by PD-L1 Expression Number (%) of patients with event*		Hazard Ratio† (95% CI)
CPS < 10	140 (75%)	144 (82%)	0.75 (0.59, 0.95)
CPS ≥ 10	53 (72%)	72 (80%)	0.55 (0.37, 0.81)

* Based on final analysis

† Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0.70; 95% CI 0.55-0.90). Over 15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-052: Open-label study in urothelial carcinoma patients ineligible for cisplatin-containing chemotherapy

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-052, a multicentre, open-label study for the treatment of locally advanced or metastatic urothelial carcinoma in patients

who were not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab at a dose of 200 mg every 3 weeks until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among 370 patients with urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-eight percent had M1 disease and 12% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: baseline creatinine clearance of < 60 mL/min (50%), ECOG performance status of 2 (32%), ECOG performance status of 2 and baseline creatinine clearance of < 60 mL/min (9%), and other (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss; 9%). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Eighty-one percent had a primary tumour in the lower tract, and 19% of patients had a primary tumour in the upper tract.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were duration of response, PFS, and OS. Table 25 summarises the key efficacy measures for the study population at the final analysis based on a median follow-up time of 11.4 months (range: 0.1, 41.2 months) for all patients.

Table 25: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma ineligible for cisplatin-containing chemotherapy in KEYNOTE-052

Endpoint	**n=370**
Objective response rate*	
ORR % (95% CI)	29% (24, 34)
Disease control rate†	47%
Complete response	9%
Partial response	20%
Stable disease	18%
Response duration	
Median in months (range)	30.1 (1.4+, 35.9+)
% with duration ≥ 6-months	81%‡
Time to response	
Median in months (range)	2.1 (1.3, 9.0)
PFS*	
Median in months (95% CI)	2.2 (2.1, 3.4)
6-month PFS rate	33%
12-month PFS rate	22%
OS	
Median in months (95% CI)	11.3 (9.7, 13.1)
6-month OS rate	67%
12-month OS rate	47%

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 84 patients with response of 6 months or longer

An analysis was performed in KEYNOTE-052 in patients who had tumours that expressed PD-L1 with a CPS < 10 (n=251; 68%) or ≥ 10 (n=110; 30%) based on the PD-L1 IHC 22C3 pharmDx™ Kit (see Table 26).

Table 26: ORR and OS by PD-L1 expression

Endpoint	**CPS < 10 n=251**	**CPS ≥ 10 n=110**
Objective response rate*		
ORR % (95% CI)	20% (16, 26)	47% (38, 57)
OS		
Median in months (95% CI)	10 (8, 12)	19 (12, 29)
12-month OS rate	41%	61%

* BICR using RECIST 1.1

KEYNOTE-361 is a Phase III, randomised, controlled, open-label clinical study of pembrolizumab with or without platinum-based combination chemotherapy (i.e. either cisplatin or carboplatin with gemcitabine) versus chemotherapy as first-line treatment in subjects with advanced or metastatic urothelial carcinoma. Results of KEYNOTE-361 for pembrolizumab in combination with chemotherapy did not show statistically significant improvement in PFS as assessed by BICR using RECIST 1.1 (HR 0.78; 95% CI: 0.65, 0.93; p=0.0033), and OS (HR 0.86; 95% CI: 0.72, 1.02; p=0.0407) versus chemotherapy alone. Per the pre-specified hierarchical testing order no formal tests for statistical significance of pembrolizumab versus chemotherapy could be performed. The key efficacy results of pembrolizumab monotherapy in patients for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy were consistent with KEYNOTE-052 results. Efficacy results in patients whose tumours express PD-L1 with CPS ≥ 10 were similar to the overall population for whom carboplatin was selected as the choice of chemotherapy. See Table 27 and Figures 21 and 22.

Table 27: Response to pembrolizumab 200 mg every 3 weeks or chemotherapy in patients with previously untreated urothelial carcinoma for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy in KEYNOTE-361

Endpoint	Pembrolizumab n=170	Chemotherapy n=196	Pembrolizumab CPS ≥ 10 n=84	Chemotherapy CPS ≥ 10 n=89
Objective response rate*				
ORR % (95% CI)	28% (21.1, 35.0)	42% (34.8, 49.1)	30% (20.3, 40.7)	46% (35.4, 57.0)
Complete response	10%	11%	12%	18%
Partial response	18%	31%	18%	28%
Response duration*				
Median in months (range)	NR (3.2+, 36.1+)	6.3 (1.8+, 33.8+)	NR (4.2, 36.1+)	8.3 (2.1+, 33.8+)
% with duration ≥ 12 months†	57%	30%	63%	38%
PFS*				
Median in months (95% CI)	3.2 (2.2, 5.5)	6.7 (6.2, 8.1)	3.9 (2.2, 6.8)	7.9 (6.1, 9.3)
12-month PFS rate	25%	24%	26%	31%
OS				
Median in months (95% CI)	14.6 (10.2, 17.9)	12.3 (10.0, 15.5)	15.6 (8.6, 19.7)	13.5 (9.5, 21.0)
12-month OS rate	54%	51%	57%	54%

* Assessed by BICR using RECIST 1.1

† Based on Kaplan-Meier estimation

NR = not reached

Figure 21: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-361 (intent to treat population, choice of carboplatin)

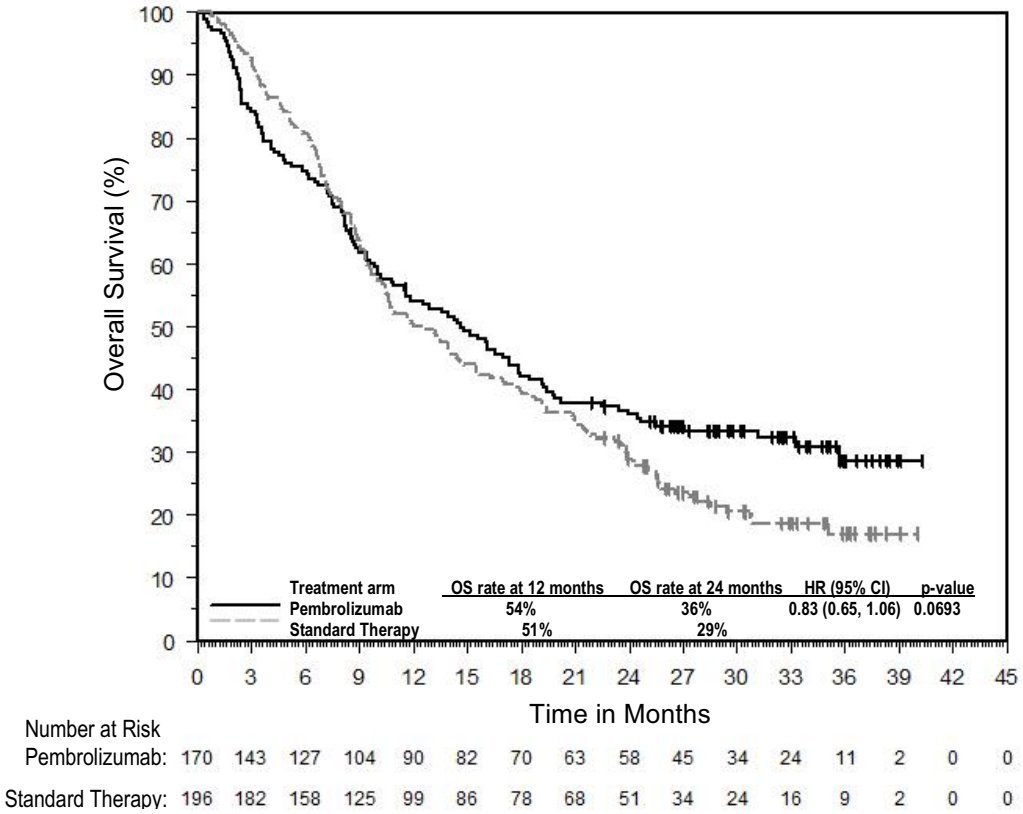
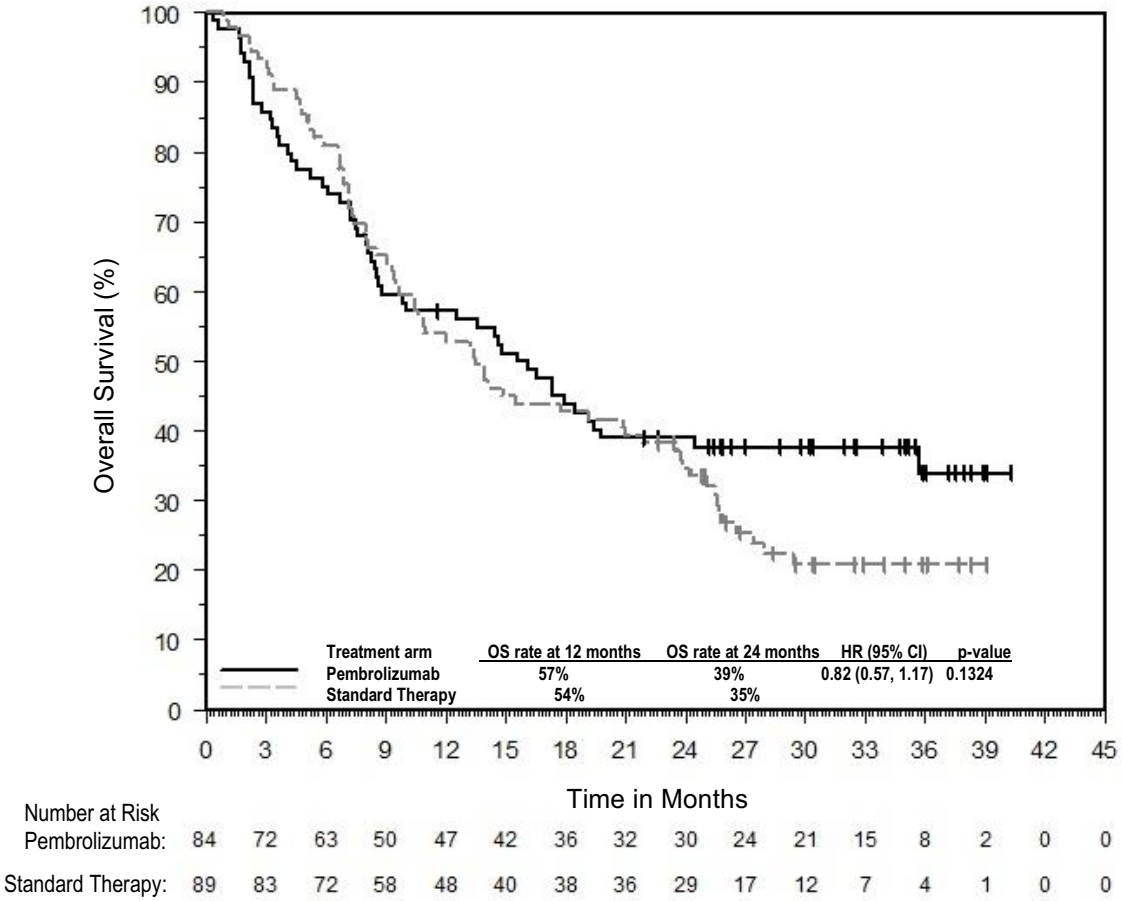


Figure 22: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-361 (patients with PD-L1 expression CPS ≥ 10, intent to treat population, choice of carboplatin)



Head and Neck Squamous Cell Carcinoma

KEYNOTE-048: Controlled study of monotherapy and combination therapy in HNSCC patients naïve to treatment in the recurrent or metastatic setting

The efficacy of pembrolizumab was investigated in KEYNOTE-048, a multicentre, randomised, open-label, active-controlled study in patients with histologically confirmed metastatic or recurrent HNSCC of the oral cavity, pharynx or larynx, who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Patients with nasopharyngeal carcinoma, active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by tumour PD-L1 expression (TPS ≥ 50% or < 50%), HPV status (positive or negative), and ECOG PS (0 vs. 1). Patients were randomised 1:1:1 to one of the following treatment arms:

- Pembrolizumab 200 mg every 3 weeks
- Pembrolizumab 200 mg every 3 weeks, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1 000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)
- Cetuximab 400 mg/m^2 load then 250 mg/m^2 once weekly, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1 000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)

Treatment with pembrolizumab continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of

tumour status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months.

Among the 882 patients in KEYNOTE-048, 754 (85%) had tumours that expressed PD-L1 with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 754 patients included: median age of 61 years (range: 20 to 94); 36% age 65 or older; 82% male; 74% White and 19% Asian; 61% ECOG performance status of 1; and 77% former/current smokers. Disease characteristics were: 21% HPV positive and 95% had stage IV disease (stage IVa 21%, stage IVb 6%, and stage IVc 69%).

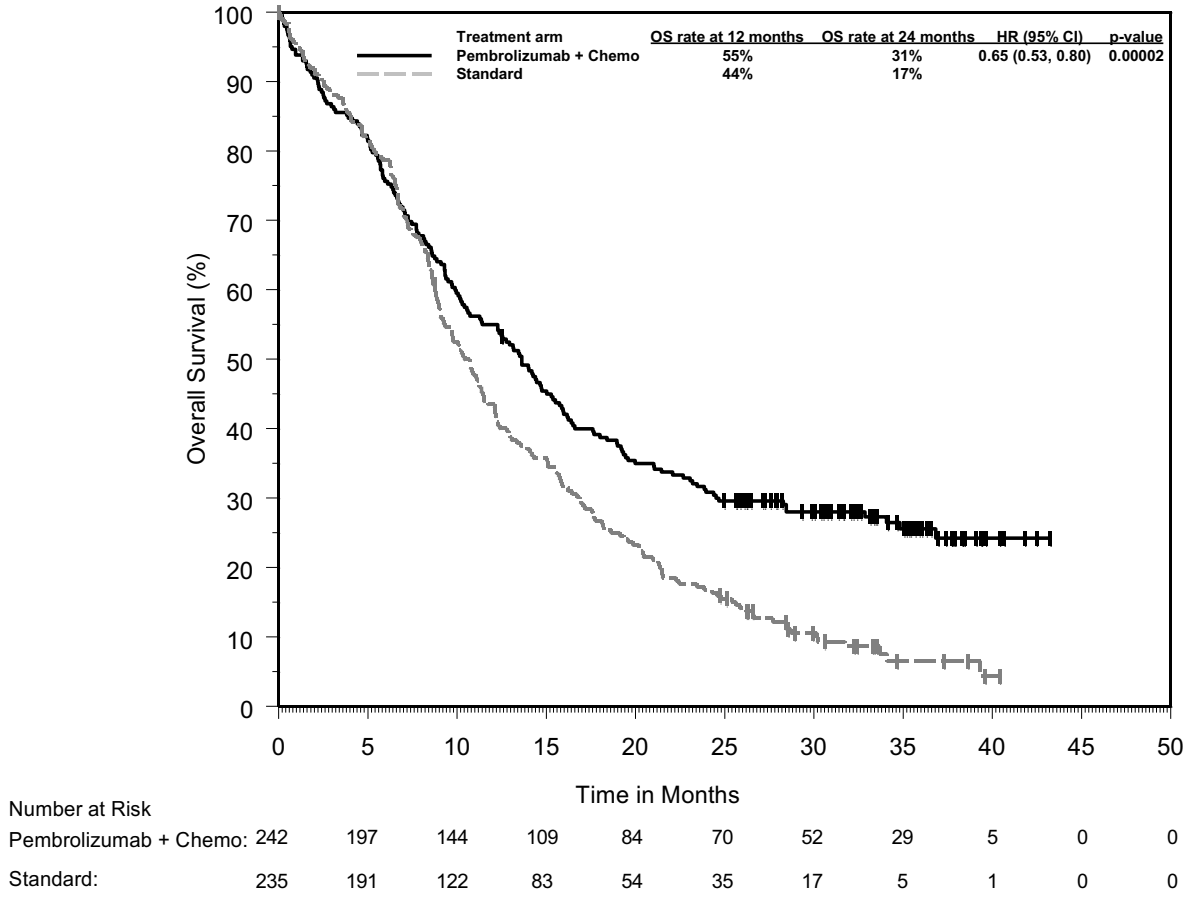
The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). The study demonstrated a statistically significant improvement in OS for all patients randomised to pembrolizumab in combination with chemotherapy compared to standard treatment (HR 0.72; 95% CI 0.60-0.87) and in patients whose tumours expressed PD-L1 CPS ≥ 1 randomised to pembrolizumab monotherapy compared to standard treatment. Tables 28 and 29 summarise key efficacy results for pembrolizumab in patients whose tumours expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-048 at the final analysis performed at a median follow-up of 13 months for pembrolizumab in combination with chemotherapy and at a median follow-up of 11.5 months for pembrolizumab monotherapy. Kaplan-Meier curves for OS based on the final analysis are shown in Figures 23 and 24.

Table 28: Efficacy results for pembrolizumab plus chemotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

Endpoint	**Pembrolizumab + Platinum Chemotherapy + 5-FU n=242**	**Standard Treatment* n=235**
OS		
Number (%) of patients with event	177 (73%)	213 (91%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
Hazard ratio† (95% CI)	0.65 (0.53, 0.80)	
p-Value‡	0.00002	
PFS		
Number (%) of patients with event	212 (88%)	221 (94%)
Median in months (95% CI)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	0.84 (0.69, 1.02)	
p-Value‡	0.03697	
Objective response rate		
ORR§ % (95% CI)	36% (30.3, 42.8)	36% (29.6, 42.2)
Complete response	7%	3%
Partial response	30%	33%
p-Value¶	0.4586	
Response duration		
Median in months (range)	6.7 (1.6+, 39.0+)	4.3 (1.2+, 31.5+)
% with duration ≥ 6 months	54%	34%

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

Figure 23: Kaplan-Meier curve for overall survival for pembrolizumab plus chemotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)



Number at Risk

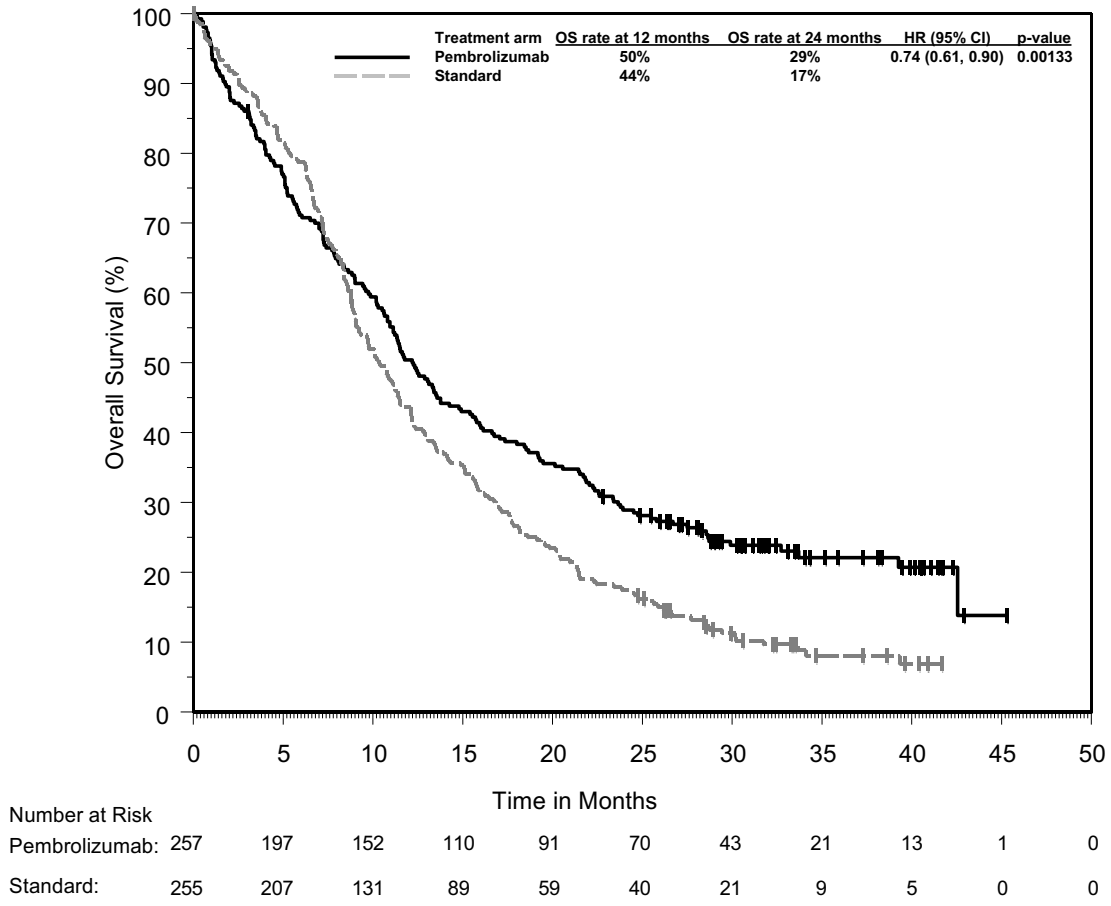
Pembrolizumab + Chemo:	242	197	144	109	84	70	52	29	5	0	0
Standard:	235	191	122	83	54	35	17	5	1	0	0

Table 29: Efficacy results for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab n=257	Standard Treatment* n=255
OS		
Number (%) of patients with event	197 (77%)	229 (90%)
Median in months (95% CI)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)
Hazard ratio† (95% CI)	0.74 (0.61, 0.90)	
p-Value‡	0.00133	
PFS		
Number (%) of patients with event	228 (89%)	237 (93%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	1.13 (0.94, 1.36)	
p-Value‡	0.89580	
Objective response rate		
ORR§ % (95% CI)	19.1% (14.5, 24.4)	35% (29.1, 41.1)
Complete response	5%	3%
Partial response	14%	32%
p-Value¶	1.0000	
Response duration		
Median in months (range)	23.4 (1.5+, 43.0+)	4.5 (1.2+, 38.7+)
% with duration ≥ 6 months	81%	36%

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

Figure 24: Kaplan-Meier curve for overall survival for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)



An analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥ 20 [pembrolizumab plus chemotherapy: n=126 (49%) vs. standard treatment: n=110 (43%) and pembrolizumab monotherapy: n=133 (52%) vs. standard treatment: n=122 (48%)] (see Table 30).

Table 30: Efficacy results for pembrolizumab plus chemotherapy and pembrolizumab as monotherapy by PD-L1 expression in KEYNOTE-048 (CPS ≥ 20)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=126	Standard Treatment* n=110	Pembrolizumab Monotherapy n=133	Standard Treatment* n=122
OS				
Number (%) of patients with event	84 (66.7%)	98 (89.1%)	94 (70.7%)	108 (88.5%)
Median in months (95% CI)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)	14.8 (11.5, 20.6)	10.7 (8.8, 12.8)
Hazard ratio† (95% CI)	0.60 (0.45, 0.82)		0.58 (0.44, 0.78)	
p-Value‡	0.00044		0.00010	
OS rate at 6 months (95% CI)	74.6 (66.0, 81.3)	80.0 (71.2, 86.3)	74.4 (66.1, 81.0)	79.5 (71.2, 85.7)
OS rate at 12 months (95% CI)	57.1 (48.0, 65.2)	46.1 (36.6, 55.1)	56.4 (47.5, 64.3)	44.9 (35.9, 53.4)
OS rate at 24 months (95% CI)	35.4 (27.2, 43.8)	19.4 (12.6, 27.3)	35.3 (27.3, 43.4)	19.1 (12.7, 26.6)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=126	Standard Treatment* n=110	Pembrolizumab Monotherapy n=133	Standard Treatment* n=122
PFS				
Number (%) of patients with event	106 (84.1%)	104 (94.5%)	115 (86.5%)	114 (93.4%)
Median in months (95% CI)	5.8 (4.7, 7.6)	5.3 (4.9, 6.3)	3.4 (3.2, 3.8)	5.3 (4.8, 6.3)
Hazard ratio† (95% CI)	0.76 (0.58, 1.01)		0.99 (0.76, 1.29)	
p-Value‡	0.02951		0.46791	
PFS rate at 6 months (95% CI)	49.4 (40.3, 57.9)	47.2 (37.5, 56.2)	33.0 (25.2, 41.0)	46.6 (37.5, 55.2)
PFS rate at 12 months (95% CI)	23.9 (16.7, 31.7)	14.0 (8.2, 21.3)	23.5 (16.6, 31.1)	15.1 (9.3, 22.2)
PFS rate at 24 months (95% CI)	14.6 (8.9, 21.5)	5.0 (1.9, 10.5)	16.8 (10.9, 23.8)	6.1 (2.7, 11.6)
Objective response rate				
ORR§ % (95% CI)	42.9 (34.1, 52.0)	38.2 (29.1, 47.9)	23.3 (16.4, 31.4)	36.1 (27.6, 45.3)
Response duration				
Number of responders	54	42	31	44
Median in months (range)	7.1 (2.1+, 39.0+)	4.2 (1.2+, 31.5+)	22.6 (2.7+, 43.0+)	4.2 (1.2+, 31.5+)

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥ 1 to < 20 [pembrolizumab plus chemotherapy: n=116 (45%) vs. standard treatment: n=125 (49%) and pembrolizumab monotherapy: n=124 (48%) vs. standard treatment: n=133 (52%)] (see Table 31).

Table 31: Efficacy results for pembrolizumab plus chemotherapy and pembrolizumab as monotherapy by PD-L1 expression in KEYNOTE-048 (CPS ≥ 1 to < 20)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=116	Standard Treatment* n=125	Pembrolizumab Monotherapy n=124	Standard Treatment* n=133
OS				
Number (%) of patients with event	93 (80.2%)	115 (92.0%)	103 (83.1%)	121 (91.0%)
Median in months (95% CI)	12.7 (9.4, 15.3)	9.9 (8.6, 11.5)	10.8 (9.0, 12.6)	10.1 (8.7, 12.1)
Hazard ratio† (95% CI)	0.71 (0.54, 0.94)		0.86 (0.66, 1.12)	
OS rate at 6 months (95% CI)	76.7 (67.9, 83.4)	77.4 (69.0, 83.8)	67.6 (58.6, 75.1)	78.0 (70.0, 84.2)
OS rate at 12 months (95% CI)	52.6 (43.1, 61.2)	41.1 (32.4, 49.6)	44.0 (35.1, 52.5)	42.4 (33.9, 50.7)
OS rate at 24 months (95% CI)	25.9 (18.3, 34.1)	14.5 (9.0, 21.3)	22.0 (15.1, 29.6)	15.9 (10.3, 22.6)
PFS				
Number (%) of patients with event	106 (91.4%)	117 (93.6%)	113 (91.1%)	123 (92.5%)
Median in months (95% CI)	4.9 (4.2, 5.3)	4.9 (3.7, 6.0)	2.2 (2.1, 2.9)	4.9 (3.8, 6.0)
Hazard ratio† (95% CI)	0.93 (0.71, 1.21)		1.25 (0.96, 1.61)	
PFS rate at 6 months (95% CI)	40.1 (31.0, 49.0)	40.0 (31.2, 48.5)	24.2 (17.1, 32.0)	41.4 (32.8, 49.7)
PFS rate at 12 months (95% CI)	15.1 (9.1, 22.4)	11.3 (6.4, 17.7)	17.5 (11.4, 24.7)	12.1 (7.2, 18.5)
PFS rate at 24 months (95% CI)	8.5 (4.2, 14.7)	5.0 (1.9, 10.1)	8.3 (4.3, 14.1)	6.3 (2.9, 11.5)
Objective response rate				
ORR‡ % (95% CI)	29.3 (21.2, 38.5)	33.6 (25.4, 42.6)	14.5 (8.8, 22.0)	33.8 (25.9,42.5)
Response duration				
Number of responders	34	42	18	45
Median in months (range)	5.6 (1.6+, 25.6+)	4.6 (1.4+, 31.4+)	NR (1.5+, 38.9+)	5.0 (1.4+, 38.7+)

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Response: Best objective response as confirmed complete response or partial response
NR = not reached

KEYNOTE-040: Controlled study in HNSCC patients previously treated with platinum-containing chemotherapy

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-040, a multicentre, open-label, randomised, controlled study for the treatment of histologically confirmed recurrent or metastatic HNSCC of the oral cavity, pharynx or larynx in patients who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy, and were not amenable to local therapy with curative intent. Patients were stratified by PD-L1 expression (TPS ≥ 50%), HPV status and ECOG performance status and then randomised (1:1) to receive either pembrolizumab 200 mg every 3 weeks (n=247) or one of three standard treatments (n=248): methotrexate 40 mg/m^2 once weekly (n=64), docetaxel 75 mg/m^2 once every 3 weeks (n=99), or cetuximab 400 mg/m^2 loading dose and then 250 mg/m^2 once weekly (n=71). Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. The study excluded patients with nasopharyngeal carcinoma, active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition

that required immunosuppression, or who were previously treated with 3 or more systemic regimens for recurrent and/or metastatic HNSCC. Assessment of tumour status was performed at 9 weeks, then every 6 weeks through Week 52, followed by every 9 weeks through 24 months.

Among the 495 patients in KEYNOTE-040, 129 (26%) had tumours that expressed PD-L1 with a TPS ≥ 50% based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 129 patients included: median age 62 years (40% age 65 or older); 81% male; 78% White, 11% Asian, and 2% Black; 23% and 77% with an ECOG performance status 0 or 1, respectively; and 19% with HPV positive tumours. Sixty-seven percent (67%) of patients had M1 disease and the majority had stage IV disease (stage IV 32%, stage IVa 14%, stage IVb 4%, and stage IVc 44%). Sixteen percent (16%) had disease progression following platinum-containing neoadjuvant or adjuvant chemotherapy, and 84% had received 1-2 prior systemic regimens for metastatic disease.

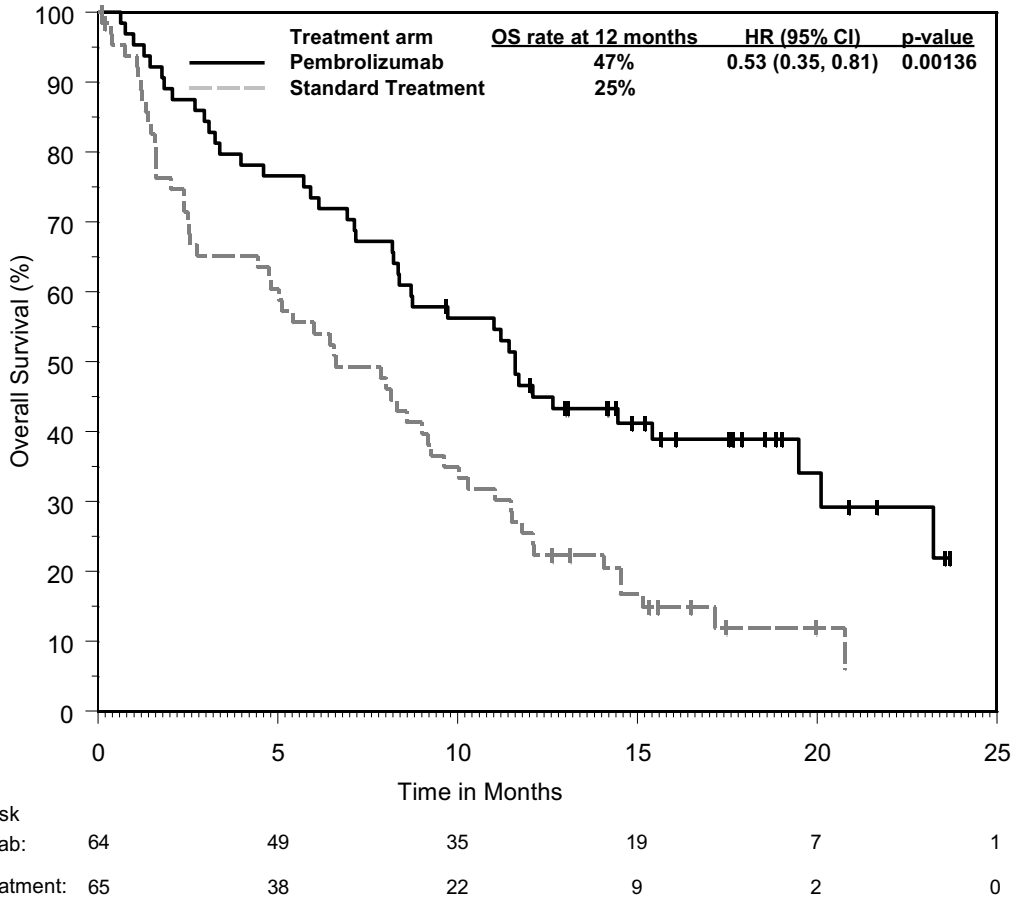
The primary efficacy outcome was OS in the ITT population. The initial analysis resulted in a HR for OS of 0.82 (95% CI: 0.67, 1.01) with a one-sided p-Value of 0.0316. The median OS was 8.4 months for pembrolizumab compared to 7.1 months for standard treatment. Table 32 summarises the key efficacy measures for the TPS ≥ 50% population. The Kaplan-Meier curve for OS for the TPS ≥ 50% population is shown in Figure 25.

Table 32: Efficacy of pembrolizumab 200 mg every 3 weeks in HNSCC patients with TPS ≥ 50% who were previously treated with platinum chemotherapy in KEYNOTE-040

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=64**	**Standard Treatment[*] n=65**
OS		
Number (%) of patients with event	41 (64%)	56 (86%)
Hazard ratio[†] (95% CI)	0.53 (0.35, 0.81)	
p-Value[‡]	0.001	
Median in months (95% CI)	11.6 (8.3, 19.5)	6.6 (4.8, 9.2)
PFS[§]		
Number (%) of patients with event	52 (81%)	58 (89%)
Hazard ratio[†] (95% CI)	0.58 (0.39, 0.86)	
p-Value[‡]	0.003	
Median in months (95% CI)	3.5 (2.1, 6.3)	2.1 (2.0, 2.4)
Rate (%) at 6 months (95% CI)	40.1 (28.1, 51.9)	17.1 (8.8, 27.7)
Objective response rate[§]		
ORR % (95% CI)	26.6 (16.3, 39.1)	9.2 (3.5, 19.0)
p-Value[¶]	0.0009	
Complete response	5%	2%
Partial response	22%	8%
Stable disease	23%	23%
Response duration[§,#]		
Median in months (range)	Not reached (2.7, 13.8+)	6.9 (4.2, 18.8)
Number (%[Þ]) of patients with duration ≥ 6 months	9 (66%)	2 (50%)

[*] Methotrexate, docetaxel, or cetuximab
[†] Hazard ratio (pembrolizumab compared to standard treatment) based on the stratified Cox proportional hazard model
[‡] One-sided p-Value based on log-rank test
[§] Assessed by BICR using RECIST 1.1
[¶] Based on method by Miettinen and Nurminen
[#] Based on patients with a best objective response as confirmed complete or partial response
[Þ] Based on Kaplan-Meier estimation

Figure 25: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-040 patients with PD-L1 expression (TPS ≥ 50%)



Renal cell carcinoma

KEYNOTE-426: Controlled study of combination therapy with axitinib in RCC patients naïve to treatment

The efficacy of pembrolizumab in combination with axitinib was investigated in KEYNOTE-426, a randomised, multicentre, open-label, active-controlled study conducted in patients with advanced RCC with clear cell component, regardless of PD-L1 tumour expression status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by risk categories (favourable versus intermediate versus poor) and geographic region (North America versus Western Europe versus "Rest of the World"). Patients were randomised (1:1) to one of the following treatment arms:

- pembrolizumab 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive treatment cycles (i.e. 6 weeks) with no > Grade 2 treatment-related adverse events to axitinib and with blood pressure well controlled to ≤ 150/90 mm Hg were permitted dose escalation of axitinib to 7 mg twice daily. Dose escalation of axitinib to 10 mg twice daily was permitted using the same criteria. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

Treatment with pembrolizumab and axitinib continued until RECIST v1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months. Administration of pembrolizumab and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was

performed at baseline, after randomisation at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter.

A total of 861 patients were randomised. The study population characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 80% had a Karnofsky Performance Score (KPS) 90-100 and 20% had KPS 70-80; patient distribution by IMDC risk categories was 31% favourable, 56% intermediate and 13% poor.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The study demonstrated a statistically significant improvement in OS (HR 0.53; 95% CI 0.38, 0.74; p-Value = 0.00005) and PFS (HR 0.69; 95% CI 0.56, 0.84; p-Value = 0.00012) for patients randomised to the pembrolizumab combination arm compared with sunitinib at its pre-specified interim analysis. Table 33 summarises key efficacy measures and Figures 26 and 27 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up time of 37.7 months.

Table 33: Efficacy results in KEYNOTE-426

Endpoint	**Pembrolizumab Axitinib n=432**	**Sunitinib n=429**
OS		
Number (%) of patients with event	193 (45%)	225 (52%)
Median in months (95% CI)	45.7 (43.6, NA)	40.1 (34.3, 44.2)
Hazard ratio* (95% CI)	0.73 (0.60, 0.88)	
p-Value†	0.00062	
PFS‡		
Number (%) of patients with event	286 (66%)	301 (70%)
Median in months (95% CI)	15.7 (13.6, 20.2)	11.1 (8.9, 12.5)
Hazard ratio* (95% CI)	0.68 (0.58, 0.80)	
p-Value†	< 0.00001	
Objective response rate		
ORR§ % (95% CI)	60 (56, 65)	40 (35, 44)
Complete response	10%	3%
Partial response	50%	36%
p-Value¶	< 0.0001	
Response duration		
Median in months (range)	23.6 (1.4+, 43.4+)	15.3 (2.3, 42.8+)
Number (%#) of patients with duration ≥ 30 months	87 (45%)	29 (32%)

* Based on the stratified Cox proportional hazard model
† Nominal p-Value based on stratified log-rank test
‡ Assessed by BICR using RECIST 1.1
§ Based on patients with a best objective response as confirmed complete or partial response
¶ Nominal p-Value based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region. At the pre-specified interim analysis of ORR (median follow-up time of 12.8 months), statistically significant superiority was achieved for ORR comparing pembrolizumab plus axitinib with sunitinib p-Value < 0.0001.
# Based on Kaplan-Meier estimation
NA = not available

Figure 26: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-426 (intent to treat population)

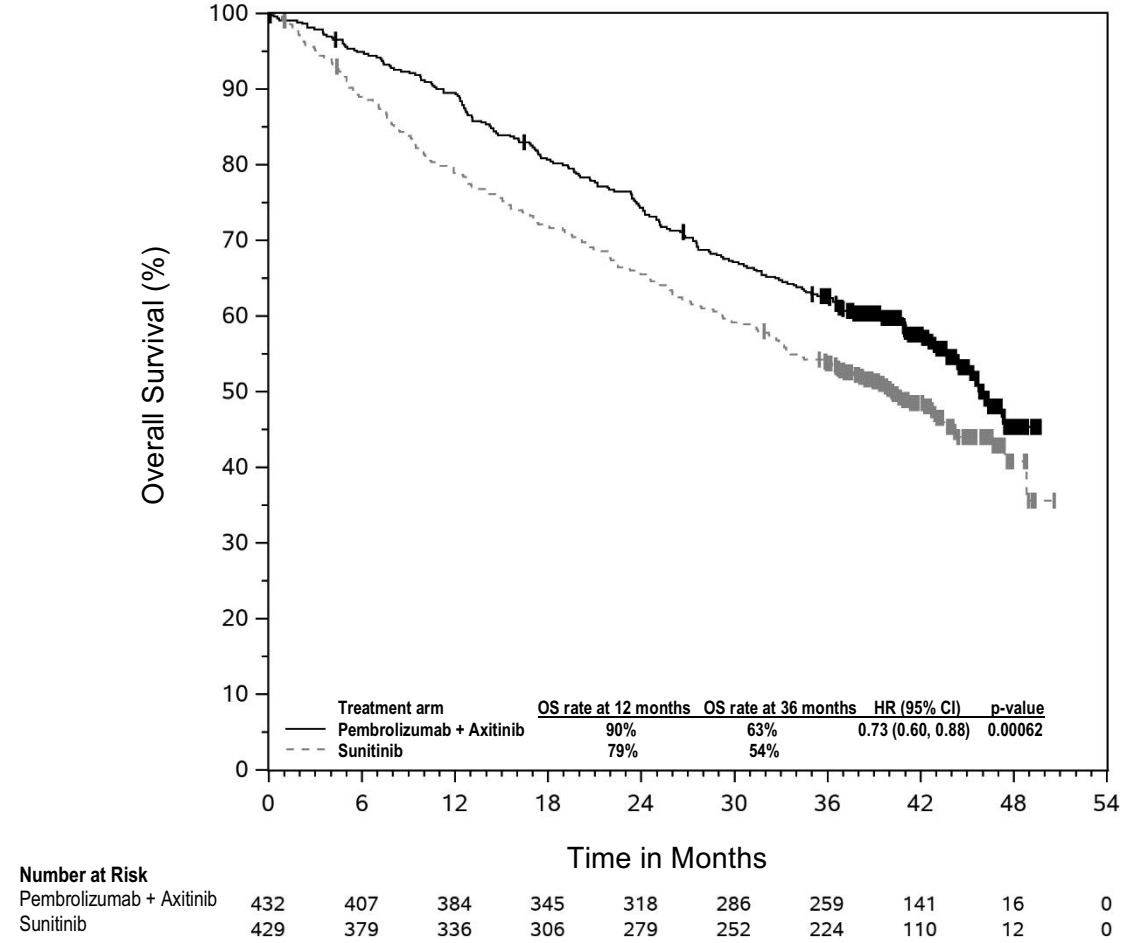
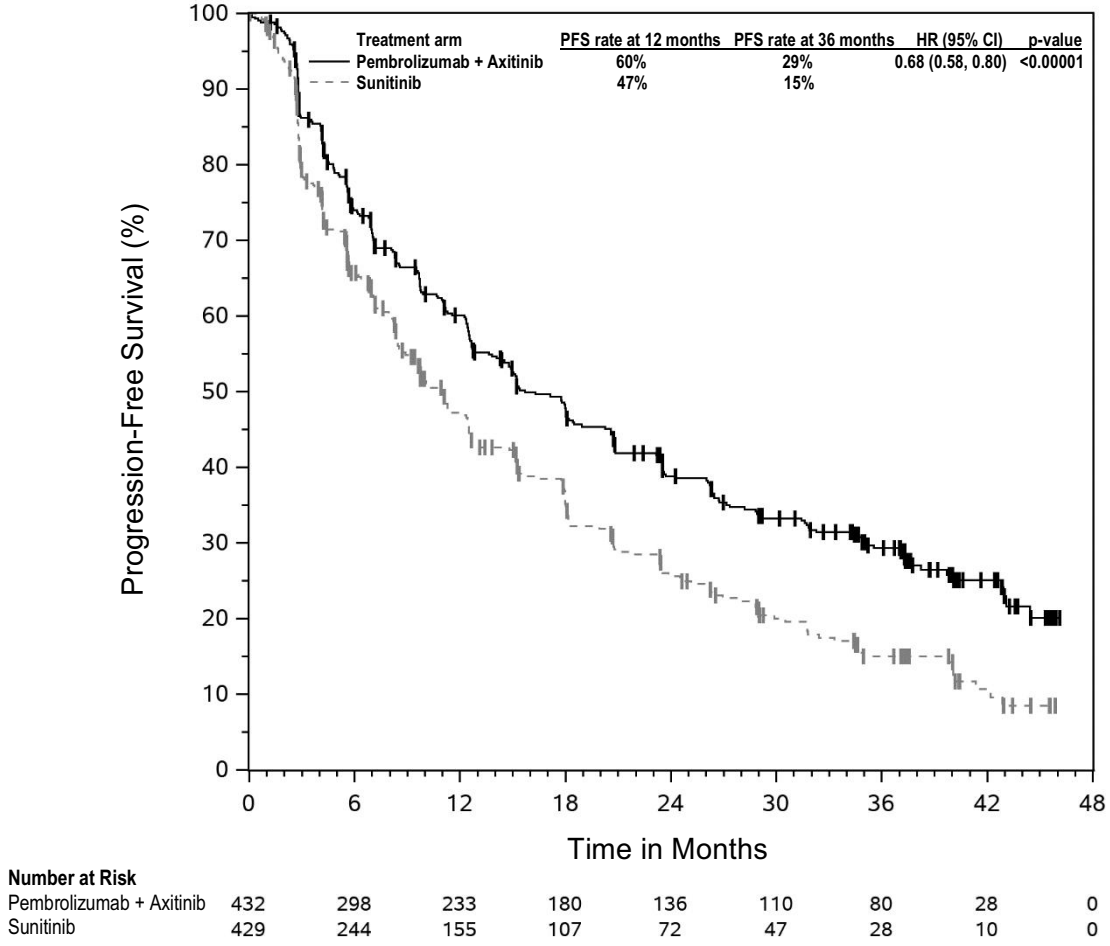


Figure 27: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-426 (intent to treat population)



Subgroup analyses were performed in KEYNOTE-426 in patients with PD-L1 CPS ≥ 1 [pembrolizumab/axitinib combination: n=243 (56%) vs. sunitinib: n=254 (59%)] and CPS < 1 [pembrolizumab/axitinib combination: n=167 (39%) vs. sunitinib: n=158 (37%)]. OS and PFS benefits were observed regardless of PD-L1 expression level.

The KEYNOTE-426 study was not powered to evaluate efficacy of individual subgroups.

Table 34 summarises the efficacy measures by IMDC risk category based on the final OS analysis at a median follow-up of 37.7 months.

Table 34: Efficacy results in KEYNOTE-426 by IMDC risk category

Endpoint*	**Pembrolizumab + Axitinib n=432**	**Sunitinib n=429**	**Pembrolizumab + Axitinib vs. Sunitinib**
OS	**12-month OS rate, % (95% CI)**		**OS HR (95% CI)**
Favourable	95.6 (90.5, 98.0)	94.6 (89.0, 97.4)	1.17 (0.76, 1.80)
Intermediate	90.7 (86.2, 93.8)	77.6 (71.8, 82.3)	0.67 (0.52, 0.86)
Poor	69.6 (55.8, 79.9)	45.1 (31.2, 58.0)	0.51 (0.32, 0.81)
PFS	**Median (95% CI), months**		**PFS HR (95% CI)**
Favourable	20.7 (15.2, 28.9)	17.8 (12.5, 20.7)	0.76 (0.56, 1.03)

Endpoint*	Pembrolizumab + Axitinib n=432	Sunitinib n=429	Pembrolizumab + Axitinib vs. Sunitinib
Intermediate	15.3 (12.5, 20.8)	9.7 (8.0, 12.4)	0.69 (0.55, 0.86)
Poor	4.9 (2.8, 12.4)	2.9 (2.7, 4.2)	0.53 (0.33, 0.84)
Confirmed ORR	**% (95% CI)**		**ORR difference, % (95% CI)**
Favourable	68.8 (60.4, 76.4)	50.4 (41.5, 59.2)	18.5 (6.7, 29.7)
Intermediate	60.5 (54.0, 66.8)	39.8 (33.7, 46.3)	20.7 (11.8, 29.2)
Poor	39.3 (26.5, 53.2)	11.5 (4.4, 23.4)	27.7 (11.7, 42.8)

* n (%) for favourable, intermediate and poor risk categories for pembrolizumab/axitinib vs. sunitinib were: 138 (32%) vs. 131 (31%); 238 (55%) vs. 246 (57%); 56 (13%) vs. 52 (12%), respectively

KEYNOTE-581 (CLEAR): Controlled study of combination therapy with lenvatinib in RCC patients naïve to treatment

The efficacy of pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-581 (CLEAR), a multicentre, open-label, randomised study conducted in 1 069 patients with advanced RCC with clear cell component including other histological features such as sarcomatoid and papillary in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. The study excluded patients with active autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by geographic region (North America versus Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favourable versus intermediate versus poor).
Patients were randomised (1:1:1) to one of the following treatment arms:

- pembrolizumab 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.
- lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BICR using RECIST 1.1. Administration of pembrolizumab with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumour status was performed at baseline and then every 8 weeks.

Among the study population (355 patients in the pembrolizumab with lenvatinib arm and 357 in the sunitinib arm), the baseline characteristics were: median age of 62 years (range: 29 to 88 years), 41% age 65 or older; 74% male; 75% White, 21% Asian, 1% Black, and 2% other races; 17% and 83% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC risk categories was 33% favourable, 56% intermediate and 10% poor, and by MSKCC prognostic groups was 27% favourable, 64% intermediate and 9% poor. Metastatic disease was present in 99% of the patients and locally advanced disease was present in 1%. Common sites of metastases in patients were lung (69%), lymph node (46%), and bone (26%).

The primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The study demonstrated statistically significant improvements in PFS (HR 0.39; 95% CI 0.32, 0.49; p-Value < 0.0001), OS (HR 0.66; 95% CI 0.49, 0.88; p-Value 0.0049), and ORR (71%; [95% CI 66, 76] vs. 36%; [95% CI 31, 41]; p-Value < 0.0001) in patients randomised to pembrolizumab in combination with lenvatinib compared with sunitinib at the pre-specified interim analysis, with a median survival follow-up time of 26.5 months, and median duration of treatment for pembrolizumab plus lenvatinib of 17.0 months. The primary OS analysis was not adjusted to account for subsequent therapies.

Efficacy results for KEYNOTE-581 (CLEAR) at the protocol-specified final analysis with median follow-up time of 49.4 months are summarised in Table 35 and Figures 28 and 29. PFS results were consistent across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumour expression status. Efficacy results by MSKCC prognostic group are summarised in Table 36.

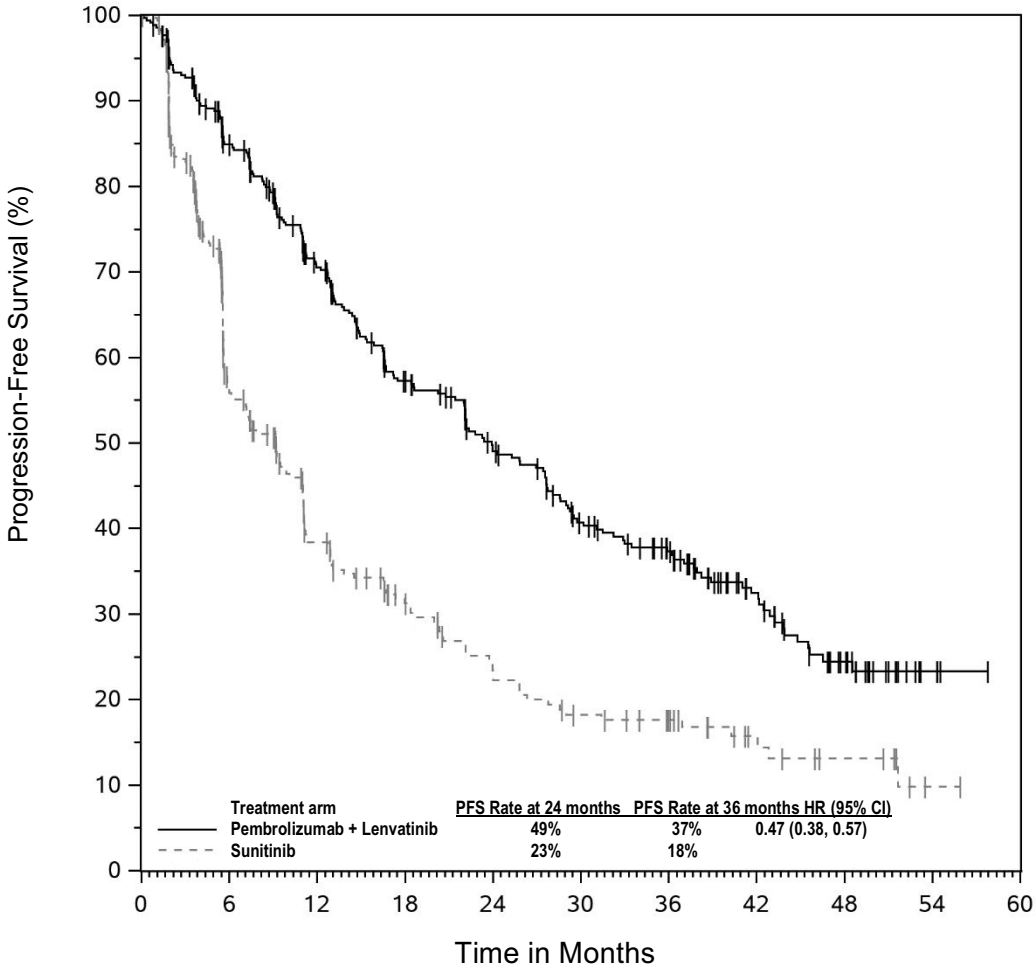
Table 35: Efficacy results in KEYNOTE-581 (CLEAR)

Endpoint	**Pembrolizumab 200 mg every 3 weeks and Lenvatinib n=355**	**Sunitinib n=357**
PFS[*]		
Number (%) of patients with event	207 (58%)	214 (60%)
Median in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio[†] (95% CI)	0.47 (0.38, 0.57)	
p-Value[‡]	< 0.0001	
OS		
Number (%) of patients with event	149 (42%)	159 (45%)
Median in months (95% CI)	53.7 (48.7, NR)	54.3 (40.9, NR)
Hazard ratio[†] (95% CI)	0.79 (0.63, 0.99)	
p-Value[‡]	0.0424	
Objective response rate		
ORR[§] % (95% CI)	71% (66.6, 76.0)	37% (31.7, 41.7)
Complete response	18%	5%
Partial response	53%	32%
p-Value[¶]	< 0.0001	
Response duration[#]		
Median in months (range)	26.7 (1.64+, 55.92+)	14.7 (1.64+, 54.08+)

[*] The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.
[†] Based on the stratified Cox proportional hazard model
[‡] Nominal p-Value, two-sided based on stratified log-rank test
[§] Response: Best objective response as confirmed complete response or partial response
[¶] Nominal two-sided p-Value based on the stratified Cochran-Mantel-Haenszel (CMH) test. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing pembrolizumab plus lenvatinib with sunitinib, (odds ratio: 3.84 [95% CI: 2.81, 5.26], p-Value < 0.0001).
[#] Based on Kaplan-Meier estimates
NR = not reached

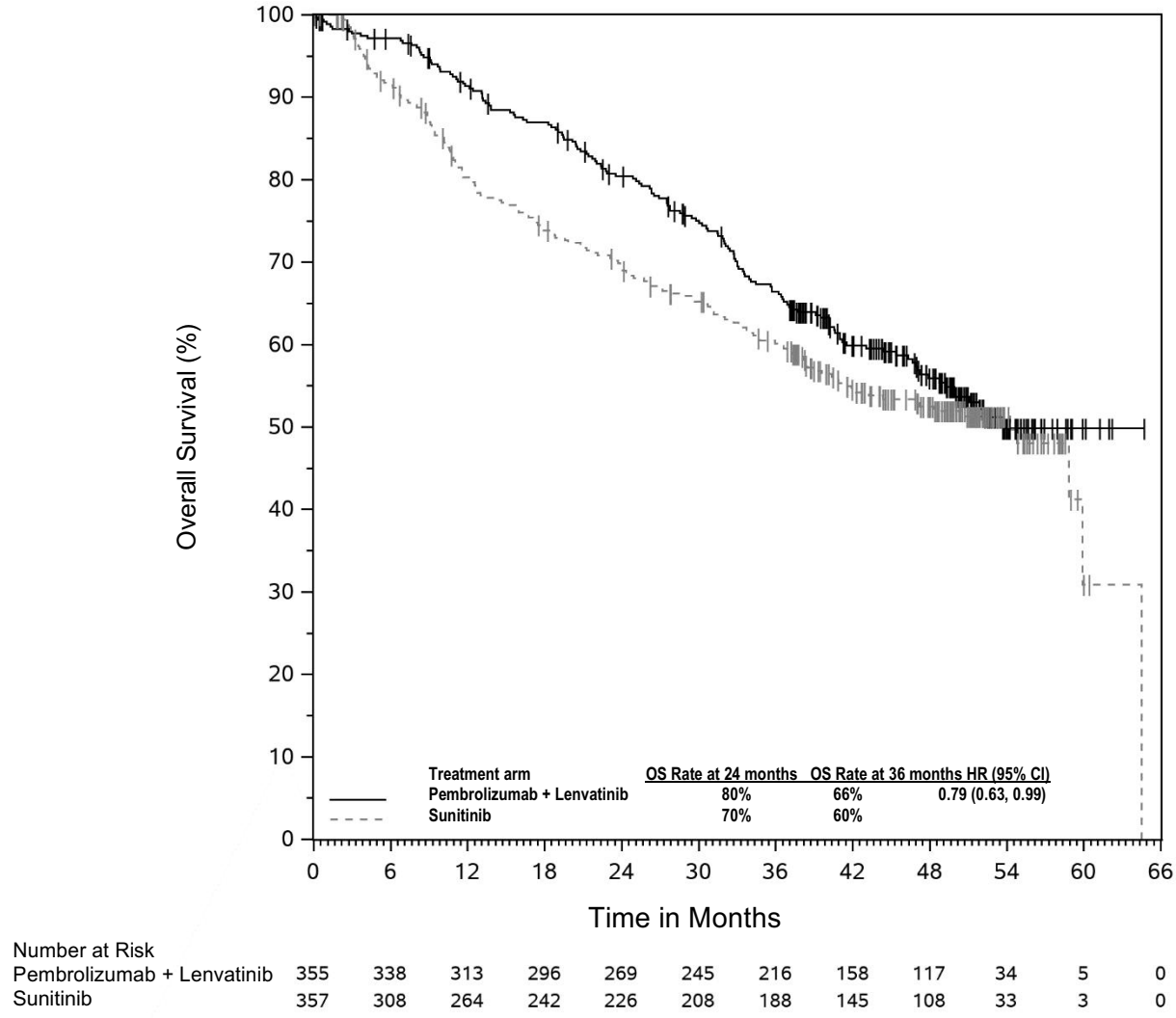
The final OS analysis was not adjusted to account for subsequent therapies, with 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the pembrolizumab plus lenvatinib arm receiving subsequent anti-PD-1/PD-L1 therapy.

Figure 28: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-581 (CLEAR)



Number at Risk											
Pembrolizumab + Lenvatinib	355	276	213	161	128	99	81	49	25	4	0
Sunitinib	357	145	85	59	41	30	23	12	7	1	0

Figure 29: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-581 (CLEAR)



The KEYNOTE-581 (CLEAR) study was not powered to evaluate efficacy of individual subgroups.

Subgroup analyses were performed by MSKCC prognostic group.
Table 36 summarises the efficacy measures by MSKCC prognostic group based on the final OS analysis at a median follow-up of 49.4 months.

Table 36: Efficacy results in KEYNOTE-581 (CLEAR) by MSKCC prognostic group

	Pembrolizumab + Lenvatinib (n=355)		Sunitinib (n=357)		Pembrolizumab + Lenvatinib vs. Sunitinib
	Number of Patients	Number of Events	Number of Patients	Number of Events	
Progression-Free Survival (PFS) by BICR*					**PFS HR (95% CI)**
Favourable	96	56	97	65	0.46 (0.32, 0.67)
Intermediate	227	129	228	130	0.51 (0.40, 0.65)
Poor	32	22	32	19	0.18 (0.08, 0.42)
Overall Survival (OS)*					**OS HR (95% CI)**
Favourable	96	27	97	31	0.89 (0.53, 1.50)
Intermediate	227	104	228	108	0.81 (0.62, 1.06)
Poor	32	18	32	20	0.59 (0.31, 1.12)

* Median follow-up: 49.4 months (data cutoff – 31 July 2022)

KEYNOTE-B61: Open-label single arm Phase II study

Additional data are available from the open-label single arm Phase II study KEYNOTE-B61 of pembrolizumab (400 mg every 6 weeks) in combination with lenvatinib (20 mg OD) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158), including 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other. The ORR was 50.6% (95% CI: 42.6, 58.7) and the median duration of response was 19.5 months (95% CI: 15.3, NR).

KEYNOTE-564: Placebo-controlled study for the adjuvant treatment of patients with resected RCC

The efficacy of pembrolizumab was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicentre, randomised, double-blind, placebo-controlled study in 994 patients with increased risk of recurrence defined as intermediate-high or high risk, or M1 with no evidence of disease (NED). The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥ 4 weeks prior to the time of screening. The study excluded patients with active autoimmune disease or a medical condition that required immunosuppression. Patients with RCC with clear cell component were randomised (1:1) to receive pembrolizumab 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year until disease recurrence or unacceptable toxicity. Randomisation was stratified by metastasis status (M0, M1 NED), and within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Starting from randomisation, patients underwent imaging every 12 weeks for the first 2 years, then every 16 weeks from year 3 to 5, and then every 24 weeks annually.

Among the 994 patients, the baseline characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent were N0; 83% had no sarcomatoid features; 86% were pT2 with Grade 4 or sarcomatoid features or pT3; 8% were pT4 or with nodal involvement; and 6% were M1 NED. Baseline characteristics and demographics were generally comparable between the pembrolizumab and placebo arms.

The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS). The key secondary outcome measure was OS. The study demonstrated statistically significant improvements in DFS and OS for patients randomised to the pembrolizumab arm compared with placebo. At the pre-specified interim analysis with a median follow-up time of 23.9 months, the DFS HR

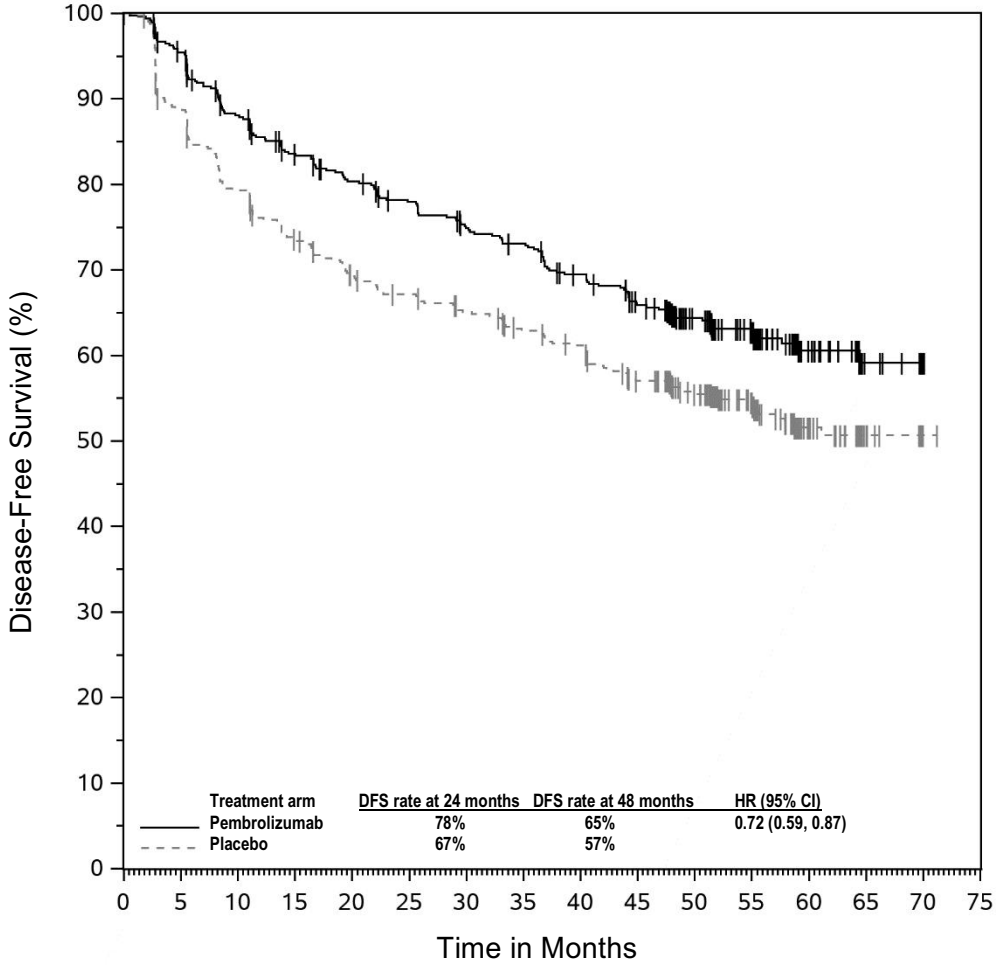
was 0.68 (95% CI 0.53, 0.87; p-Value = 0.0010). Efficacy results with a median follow-up time of 55.8 months are summarised in Table 37 and Figures 30 and 31.

Table 37: Efficacy results in KEYNOTE-564

Endpoint	Pembrolizumab 200 mg every 3 weeks n=496	Placebo n=498
DFS		
Number (%) of patients with event	174 (35%)	224 (45%)
Median in months (95% CI)	NR (NR, NR)	NR (54.9, NR)
Hazard ratio* (95% CI)	0.72 (0.59, 0.87)	
OS		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.62 (0.44, 0.87)	
p-Value†	0.0024	

* Based on the stratified Cox proportional hazard model
† One-sided p-Value based on stratified log-rank test
NR = not reached

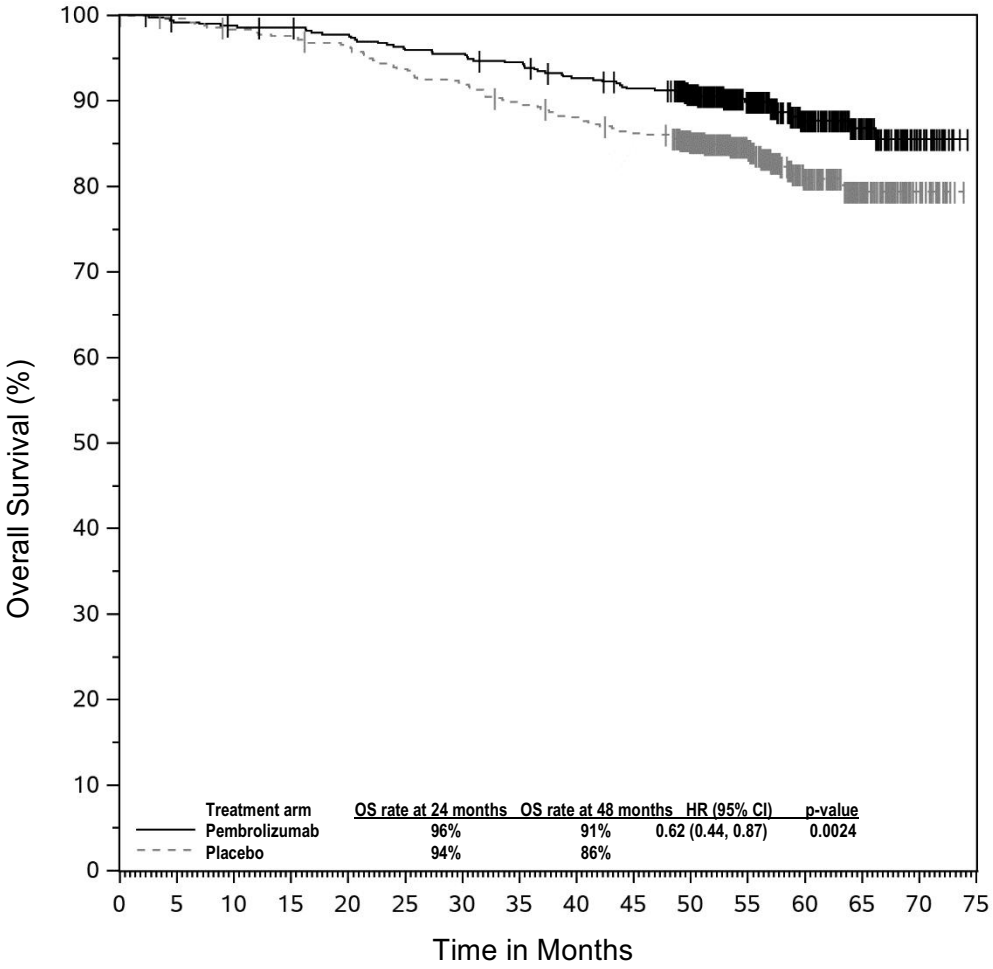
Figure 30: Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-564 (intent to treat population)



Number at Risk

Pembrolizumab	496	458	416	388	370	355	337	327	307	284	221	160	65	19	5	0
Placebo	498	438	390	357	333	320	307	292	282	254	210	139	62	16	2	0

Figure 31: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-564 (intent to treat population)



Number at Risk

Pembrolizumab	496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo	498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

MSI-H or dMMR cancers

Colorectal cancer

KEYNOTE-177: Controlled study in MSI-H or dMMR CRC patients naïve to treatment in the metastatic setting

The efficacy of pembrolizumab was investigated in KEYNOTE-177, a multicentre, randomised, open-label, active-controlled study that enrolled patients with previously untreated metastatic MSI-H or dMMR CRC. MSI or MMR (mismatch repair) tumour status was determined locally using polymerase chain reaction (PCR) or IHC, respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomised (1:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2 400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg bw on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2 400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg bw on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with pembrolizumab without disease progression could be treated for up to 24 months. Assessment of tumour status was performed every 9 weeks. Patients randomised to chemotherapy were offered pembrolizumab at the time of disease progression.

A total of 307 patients were enrolled and randomised to pembrolizumab (n=153) or chemotherapy (n=154). The baseline characteristics of these patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% and 48% had an ECOG performance status of 0 or 1, respectively. Mutation status: 25% BRAF V600E, 24% KRAS/NRAS. For 143 patients treated with chemotherapy, 56% received mFOLFOX6 with or without bevacizumab or cetuximab and 44% received FOLFIRI with or without bevacizumab or cetuximab.

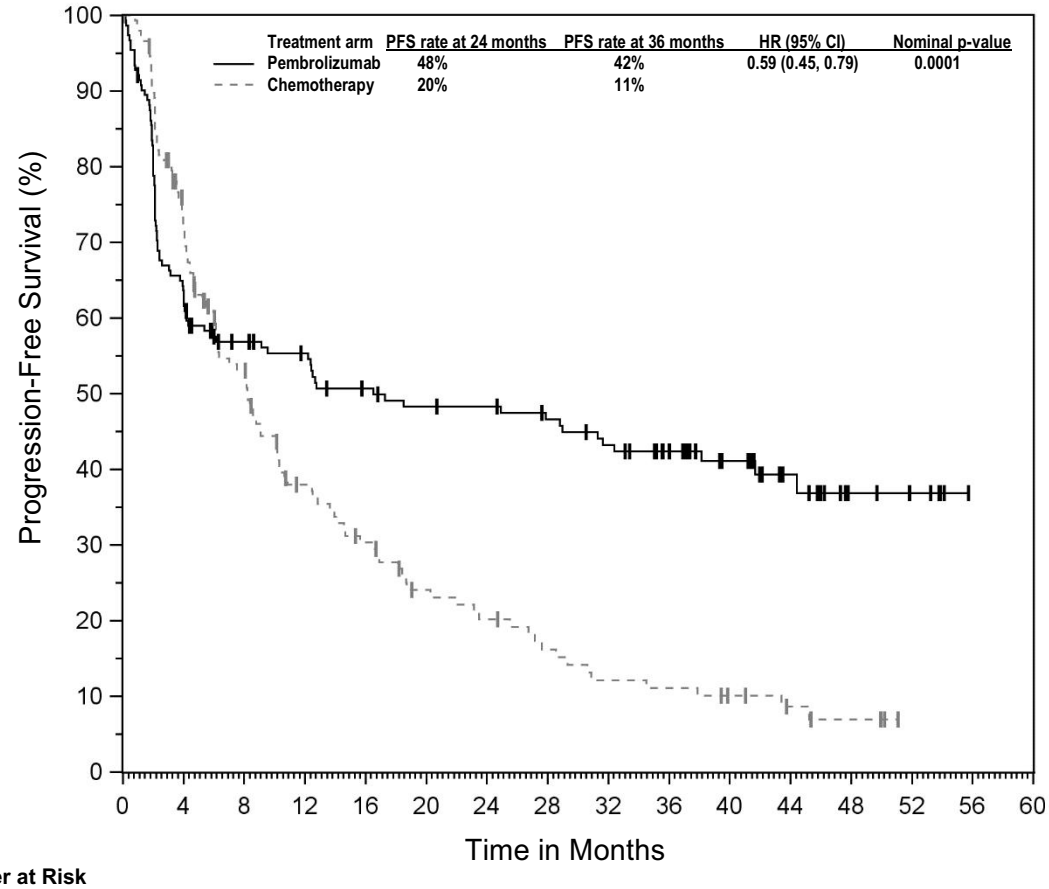
The primary efficacy outcome measures were PFS assessed by BICR according to RECIST v1.1 and OS. Secondary outcome measures were ORR and response duration. The study demonstrated a statistically significant improvement in PFS (HR 0.60; 95% CI 0.45, 0.80; p-Value 0.0002) for patients randomised to the pembrolizumab arm compared with chemotherapy at the pre-specified final analysis for PFS. There was no statistically significant difference between pembrolizumab and chemotherapy in the final OS analysis in which 60% of the patients who had been randomised to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including pembrolizumab. Table 38 summarises the key efficacy measures and Figures 32 and 33 show the Kaplan-Meier curves for updated PFS and OS based on the final analysis with a median follow-up time of 38.1 months (range: 0.2 to 58.7 months).

Table 38: Efficacy results in KEYNOTE-177

Endpoint	Pembrolizumab 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS[*]		
Number (%) of patients with event	86 (56%)	117 (76%)
Median in months (95% CI)	16.5 (5.4, 38.1)	8.2 (6.1, 10.2)
Hazard ratio[†] (95% CI)	0.59 (0.45, 0.79)	
p-Value[‡]	0.0001	
OS[§]		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio[†] (95% CI)	0.74 (0.53, 1.03)	
p-Value[§]	0.0359	
Objective response rate		
ORR % (95% CI)	45% (37.1, 53.3)	33% (25.8, 41.1)
Complete response	13%	4%
Partial response	32%	29%
Response duration		
Median in months (range)	NR (2.3+, 53.5+)	10.6 (2.8, 48.3+)
% with duration ≥ 24 months[¶]	84%	34%

[*] With additional 12 months of follow-up after the pre-specified final analysis for PFS.
[†] Based on Cox regression model
[‡] p-Value is nominal.
[§] Not statistically significant after adjustment for multiplicity
[¶] Based on Kaplan-Meier estimation
NR = not reached

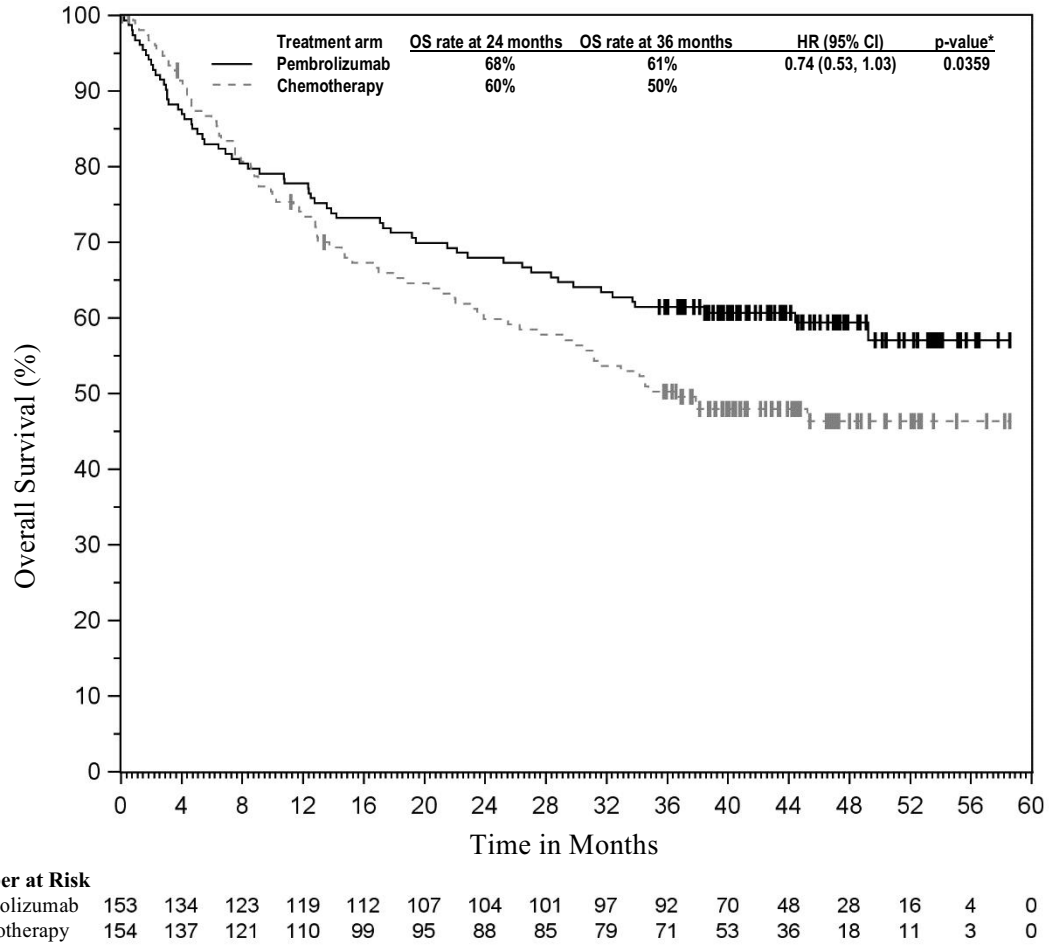
Figure 32: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-177 (intent to treat population)



Number at Risk

Pembrolizumab	153	96	77	72	64	60	59	55	50	42	28	16	7	5	0	0
Chemotherapy	154	101	69	45	35	25	21	16	12	11	8	5	3	0	0	0

Figure 33: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-177 (intent to treat population)



* Not statistically significant after adjustment for multiplicity

KEYNOTE-164: Open-label study in patients with unresectable or metastatic MSI-H or dMMR CRC who have received prior therapy

The efficacy of pembrolizumab was investigated in KEYNOTE-164, a multicentre, non-randomised, open-label, multi-cohort Phase II study that enrolled patients with unresectable or metastatic MSI-H or dMMR CRC that progressed following prior fluoropyrimidine-based therapy in combination with irinotecan and/or oxaliplatin.

Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months (up to 35 cycles). Assessment of tumour status was performed every 9 weeks.

Among the 124 patients enrolled in KEYNOTE-164, the baseline characteristics were: median age 56 years (35% age 65 or older); 56% male; 68% White, 27% Asian; 41% and 59% had an ECOG performance status of 0 and 1, respectively. Twelve percent of patients had BRAF mutations and 36% had RAS mutations; 39% and 34% were undetermined for BRAF and RAS mutations, respectively. Ninety-seven percent of the patients had M1 disease and 3% had M0 disease (locally advanced unresectable). Seventy-six percent of patients received 2 or more prior lines of therapy.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included response duration, PFS, and OS. The median follow-up time in months was 37.3 (range: 0.1 to 65.2). Efficacy results are summarised in Table 39.

Table 39: Efficacy results in KEYNOTE-164

Endpoint	n=124
Objective response rate*	
ORR % (95% CI)	34% (25.6, 42.9)
Complete response	10%
Partial response	24%
Response duration*	
Median in months (range)	NR (4.4, 58.5+)
% with duration ≥ 36 months#	92%

* Based on patients with a best objective response as confirmed complete or partial response

\# Based on Kaplan-Meier estimation

\+ Denotes there is no progressive disease by the time of last disease assessment

NR = not reached

Objective responses were observed regardless of BRAF or RAS mutation status.

Non-colorectal cancers

KEYNOTE-158: Open-label study in patients with unresectable or metastatic MSI-H or dMMR endometrial, gastric, small intestine, or biliary cancer who have received prior therapy

The efficacy of pembrolizumab was investigated in 355 patients with unresectable or metastatic MSI-H or dMMR non-CRC solid tumours enrolled in a multicentre, non-randomised, open-label Phase II study (KEYNOTE-158), including patients with endometrial, gastric, small intestine, or biliary cancer. MSI or MMR tumour status was determined prospectively using PCR or IHC, respectively.

Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months (up to 35 cycles). Assessment of tumour status was performed every 9 weeks through the first year, then every 12 weeks thereafter.

Among the 83 patients with endometrial cancer, the baseline characteristics were: median age of 64 years (range: 42 to 86), 46% age 65 or older; 84% White, 6% Asian, and 4% Black; and ECOG PS 0 (46%) and 1 (54%). Ninety-eight percent of the patients had M1 disease and 2% had M0 disease. Forty-seven percent of patients received 2 or more prior lines of therapy.

Among the 51 patients with gastric cancer, the baseline characteristics were: median age 67 years (range: 41 to 89); 57% age 65 or older; 65% male, 63% White, 28% Asian; and ECOG PS 0 (45%) and 1 (55%). All patients had M1 disease. Forty-five percent of patients received 2 or more prior lines of therapy.

Among the 27 patients with small intestinal cancer, the baseline characteristics were: median age 58 years (range: 21 to 77); 33% age 65 or older; 63% male, 81% White, 11% Asian; and ECOG PS 0 (56%) and 1 (44%). Ninety-six percent of patients had M1 disease and 4% M0 disease. Thirty-seven percent of patients received 2 or more prior lines of therapy. All patients had a tumour histology of adenocarcinoma.

Among the 22 patients with biliary cancer, the baseline characteristics were: median age 61 years (range: 40 to 77); 41% age 65 or older; 73% male, 91% White, 9% Asian; ECOG PS 0 (45%) and 1 (55%); and 82% M1 disease and 18% M0 disease. Forty-one percent of patients received 2 or more prior lines of therapy.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included response duration, PFS, and OS. The median follow-up time in

months was 21.9 (range: 1.5 to 64.0) for endometrial, 13.9 (range: 1.1 to 66.9) for gastric, 29.1 (4.2 to 67.7) for small intestine, and 19.4 (range: 1.1 to 60.8) for biliary cancer. Efficacy results are summarised in Table 40.

Table 40: Efficacy results in KEYNOTE-158

Endpoint	Endometrial n=83	Gastric n=51	Small Intestine n=27	Biliary n=22
Objective response rate*				
ORR % (95% CI)	51% (39.4, 61.8)	37% (24.1, 51.9)	56% (35.3, 74.5)	41% (20.7, 63.6)
Complete response	16%	14%	15%	14%
Partial response	35%	24%	41%	27%
Response duration*				
Median in months (range)	NR (2.9, 60.4+)	NR (6.2, 63.0+)	NR (3.7+, 57.3+)	30.6 (6.2, 46.0+)
% with duration ≥ 12 months#	85%	90%	93%	89%
% with duration ≥ 36 months#	60%	81%	73%	42%

* Based on patients with a best objective response as confirmed complete or partial response
\# Based on Kaplan-Meier estimation
\+ Denotes there is no progressive disease by the time of last disease assessment
NR = not reached

Oesophageal carcinoma

KEYNOTE-590: Controlled study of combination therapy in oesophageal carcinoma patients naïve to treatment

The efficacy of pembrolizumab in combination with chemotherapy was investigated in KEYNOTE-590, a multicentre, randomised, double-blind, placebo-controlled study in patients with locally advanced unresectable or metastatic oesophageal carcinoma or GEJ carcinoma (Siewert type I). Patients with active autoimmune disease, a medical condition that required immunosuppression, or known HER-2 positive GEJ adenocarcinoma patients were ineligible for the study. Randomisation was stratified by tumour histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomised (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration.

Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Patients randomised to pembrolizumab were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Assessment of tumour status was performed every 9 weeks.

Among the 749 patients in KEYNOTE-590, 383 (51%) had tumours that expressed PD-L1 with a CPS ≥ 10 based on the PD-L1 IHC 22C3 pharmDx^{TM} Kit. The baseline characteristics of these 383 patients were: median age of 63 years (range: 28 to 89), 41% age 65 or older; 82% male; 34% White and 56% Asian; 43% and 57% had an ECOG performance status of 0 and 1, respectively. Ninety-three percent had M1 disease. Seventy-five percent had a tumour histology of squamous cell carcinoma, and 25% had adenocarcinoma.

The primary efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST 1.1 in squamous cell histology, CPS ≥ 10, and in all patients. The study demonstrated a statistically significant improvement in OS and PFS for all pre-specified study populations. In all patients randomised to pembrolizumab in combination with chemotherapy, compared to chemotherapy the OS HR was 0.73 (95% CI 0.62-0.86) and the PFS HR was 0.65 (95% CI 0.55-0.76). Secondary efficacy outcome measures were ORR and duration of response, according to RECIST 1.1 as assessed by the investigator. Table 41 summarises key efficacy measures from the pre-specified analysis in patients whose tumours expressed PD-L1 with a CPS ≥ 10 in KEYNOTE-590 performed at a median follow-up time of 13.5 months (range: 0.5 to 32.7 months). The Kaplan-Meier curve for OS and PFS are shown in Figures 34 and 35.

Table 41: Efficacy results for pembrolizumab plus chemotherapy in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

Endpoint	**Pembrolizumab Cisplatin Chemotherapy 5-FU n=186**	**Standard Treatment[*] n=197**
OS		
Number (%) of patients with event	124 (66.7%)	165 (83.8%)
Median in months[†] (95% CI)	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)
Hazard ratio[‡] (95% CI)	0.62 (0.49, 0.78)	
p-Value[§]	< 0.0001	
PFS[¶]		
Number (%) of patients with event	140 (75.3%)	174 (88.3%)
Median in months[†] (95% CI)	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)
Hazard ratio[‡] (95% CI)	0.51 (0.41, 0.65)	
p-Value[§]	< 0.0001	
Objective response rate[¶]		
ORR[§] % (95% CI)	51.1 (43.7, 58.5)	26.9 (20.8, 33.7)
Complete response	5.9%	2.5%
Partial response	45.2%	24.4%
p-Value[#]	< 0.0001	
Response duration[¶,Þ]		
Median in months (range)	10.4 (1.9, 28.9+)	5.6 (1.5+, 25.0+)
% with duration ≥ 6 months[†]	80.2%	47.7%
% with duration ≥ 12 months[†]	43.7%	23.2%
% with duration ≥ 18 months[†]	33.4%	10.4%

[*] Cisplatin and 5-FU
[†] Based on Kaplan-Meier estimation
[‡] Based on the stratified Cox proportional hazard model
[§] One-sided p-Value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1)
[¶] Assessed by investigator using RECIST 1.1
[#] One-sided p-Value for testing. H0: difference in % = 0 versus H1: difference in % > 0
[Þ] Best objective response as confirmed complete response or partial response.

A total of 32 patients aged ≥ 75 years for PD-L1 CPS ≥ 10 were enrolled in KEYNOTE-590 (18 in the pembrolizumab combination and 14 in the control). Data about efficacy of pembrolizumab in combination with chemotherapy are too limited in this patient population.

Figure 34: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

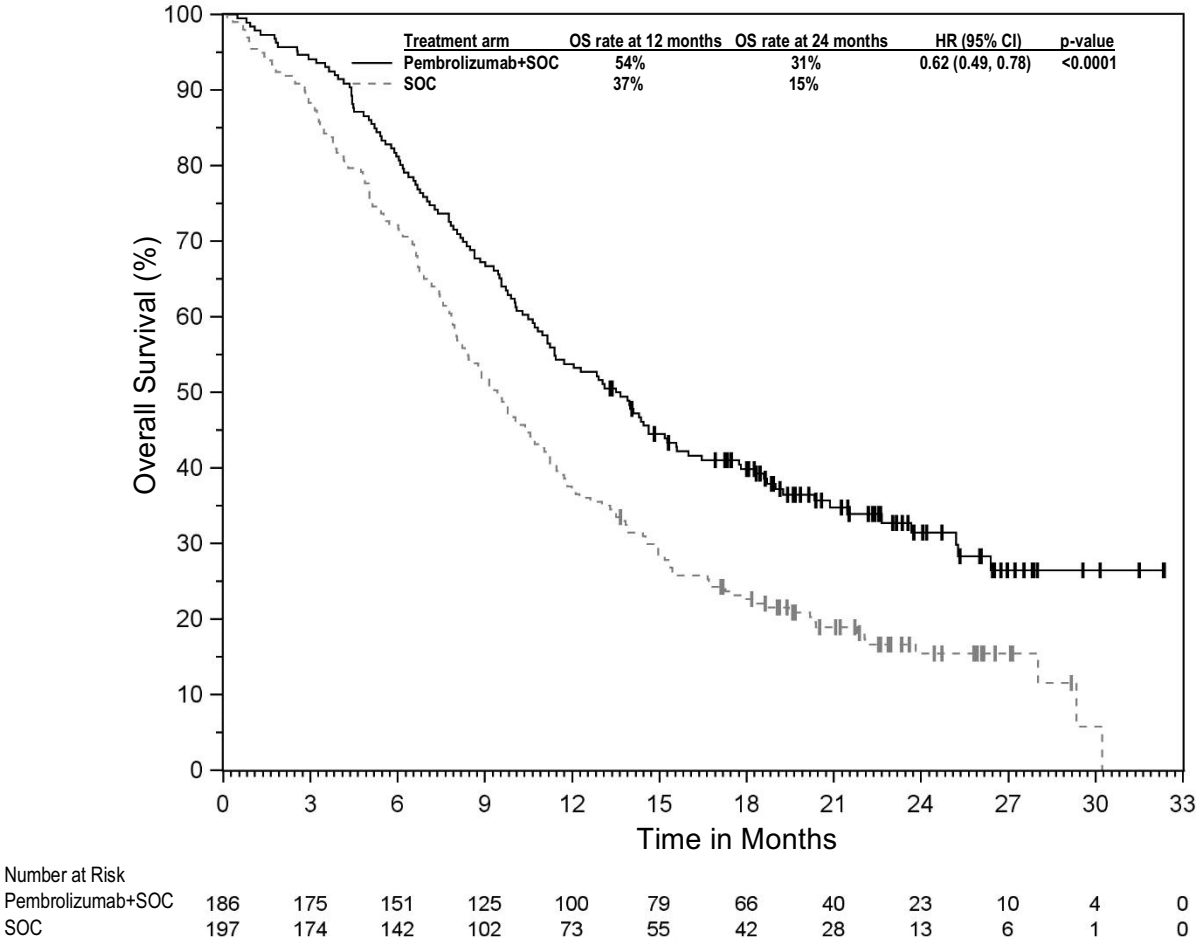
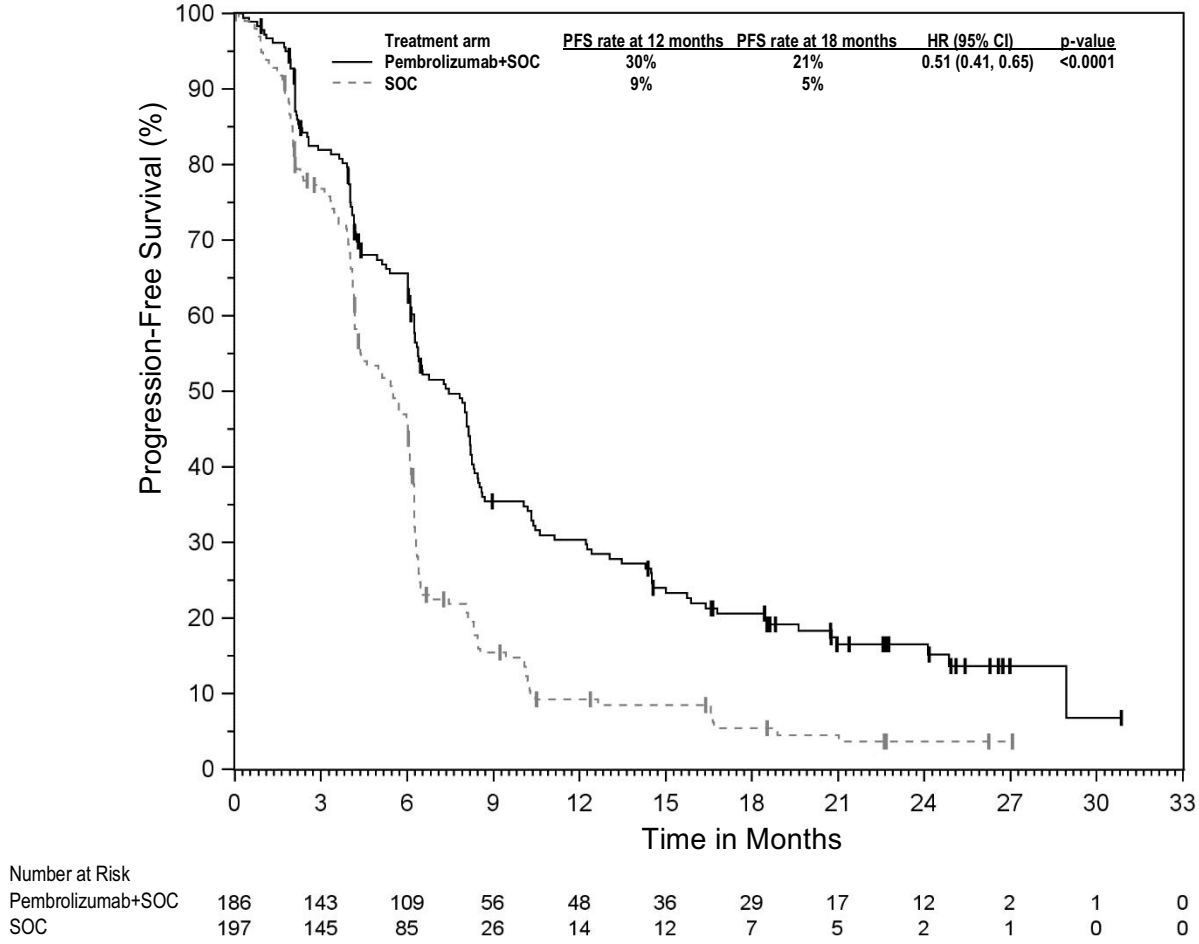


Figure 35: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



Triple-negative breast cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant therapy in patients with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high risk of recurrence

The efficacy of pembrolizumab in combination with chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment after surgery was investigated in the randomised, double-blind, multicentre, placebo-controlled study KEYNOTE-522. If indicated, patients received adjuvant radiation therapy prior to or concurrent with adjuvant pembrolizumab or placebo. The key eligibility criteria for this study were locally advanced, inflammatory, or early-stage TNBC at high risk of recurrence (tumour size > 1 cm but ≤ 2 cm in diameter with nodal involvement or tumour size > 2 cm in diameter regardless of nodal involvement), regardless of tumour PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly). Patients were randomised (2:1) to receive either pembrolizumab or placebo via intravenous infusion:

- Four cycles of neoadjuvant pembrolizumab 200 mg every 3 weeks or placebo on Day 1 of cycles 1-4 of treatment regimen in combination with:
  - Carboplatin
    - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**

- Paclitaxel 80 mg/m^2 every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen

- Followed by four additional cycles of neoadjuvant pembrolizumab 200 mg every 3 weeks or placebo on Day 1 of cycles 5-8 of treatment regimen in combination with:
  - Doxorubicin 60 mg/m^2 **or** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
  - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, 9 cycles of adjuvant pembrolizumab 200 mg every 3 weeks or placebo were administered.

Treatment with pembrolizumab or placebo continued until completion of the treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase, or unacceptable toxicity.

A total of 1 174 patients were randomised. The study population characteristics were: median age of 49 years (range: 22 to 80); 11% age 65 or older; 99.9% female; 64% White; 20% Asian, 5% Black, and 2% American Indian or Alaska Native; ECOG performance status of 0 (87%) and 1 (13%); 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumour 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 1.4% of patients had inflammatory breast cancer; 75% of patients were overall Stage II and 25% were Stage III.

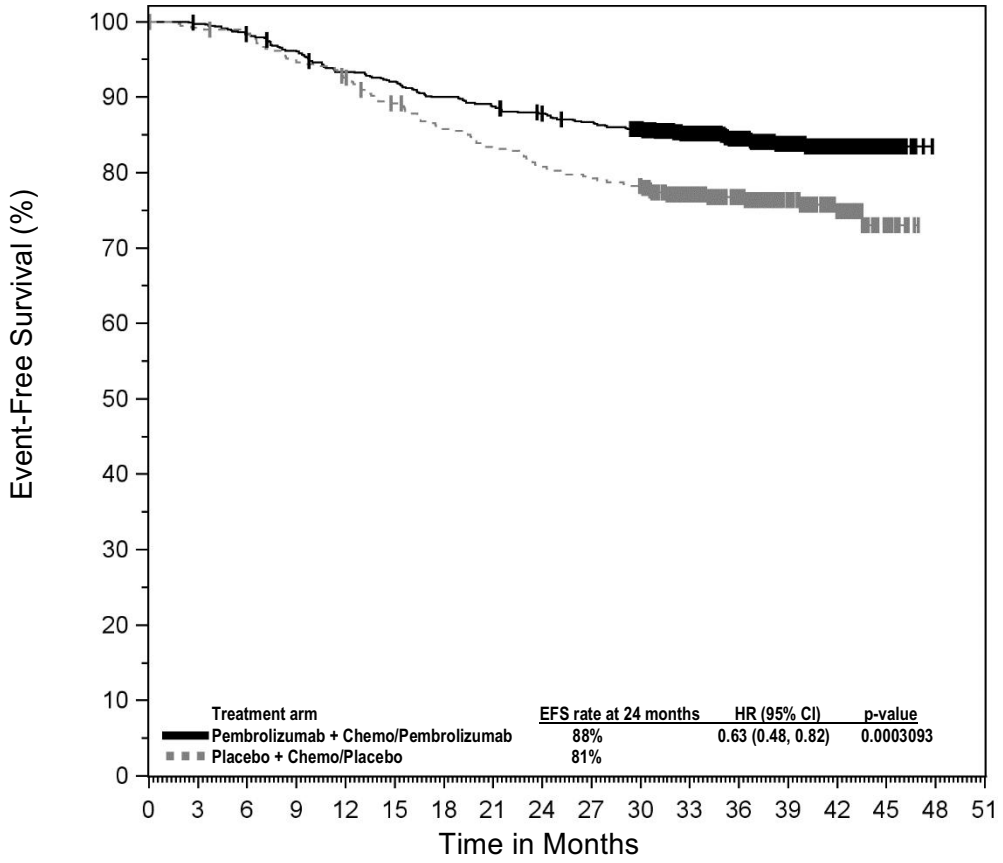
The dual primary efficacy outcome measures were pathological complete response (pCR) rate and event-free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. The study demonstrated a statistically significant improvement in pCR rate difference at its pre-specified primary analysis (n=602), the pCR rates were 64.8% (95% CI: 59.9%, 69.5%) in the pembrolizumab arm and 51.2 % (95% CI: 44.1%, 58.3%) in the placebo arm, with a treatment difference of 13.6 % (95% CI: 5.4%, 21.8%; p-Value 0.00055). The study also demonstrated a statistically significant improvement in EFS at its pre-specified analysis. A secondary efficacy outcome measure was OS. At the time of EFS analysis, OS results were not yet mature (45% of the required events for final analysis). At a pre-specified interim analysis, the median follow-up time for all patients was 37.8 months (range: 2.7-48 months). Table 42 summarises key efficacy measures from the pre-specified analyses. The Kaplan-Meier curve for EFS and OS are shown in Figures 36 and 37.

Table 42: Efficacy results in KEYNOTE-522

Endpoint	Pembrolizumab with Chemotherapy/Pembrolizumab	Placebo with Chemotherapy/Placebo
pCR (ypT0/Tis ypN0)*	**n=669**	**n=333**
Number of patients with pCR	428	182
pCR Rate (%) (95% CI)	64.0 (60.2, 67.6)	54.7 (49.1, 60.1)
Treatment difference (%) estimate (95% CI)†	9.2 (2.8, 15.6)	
p-Value‡	0.00221	
EFS§	**n=784**	**n=390**
Number (%) of patients with event	123 (15.7%)	93 (23.8%)
24 month EFS rate (95% CI)	87.8 (85.3, 89.9)	81.0 (76.8, 84.6)
Hazard ratio (95% CI)¶	0.63 (0.48, 0.82)	
p-Value#	0.00031	
OSÞ		
Number (%) of patients with event	80 (10.2%)	55 (14.1%)
24-month OS rate (95% CI)	92.3 (90.2, 94.0)	91.0 (87.7, 93.5)
Hazard ratio (95% CI)¶	0.72 (0.51, 1.02)	

* Based on a pre-specified pCR final analysis (compared to a significance level of 0.0028)
† Based on Miettinen and Nurminen method stratified by nodal status, tumour size, and choice of carboplatin
‡ One-sided p-Value for testing. H0: difference in % = 0 versus H1: difference in % > 0
§ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052)
¶ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status, tumour size, and choice of carboplatin
# One-sided p-Value based on log-rank test stratified by nodal status, tumour size, and choice of carboplatin
Þ OS results at interim analysis did not meet the pre-specified efficacy boundary of 0.00085861 for statistical significance.

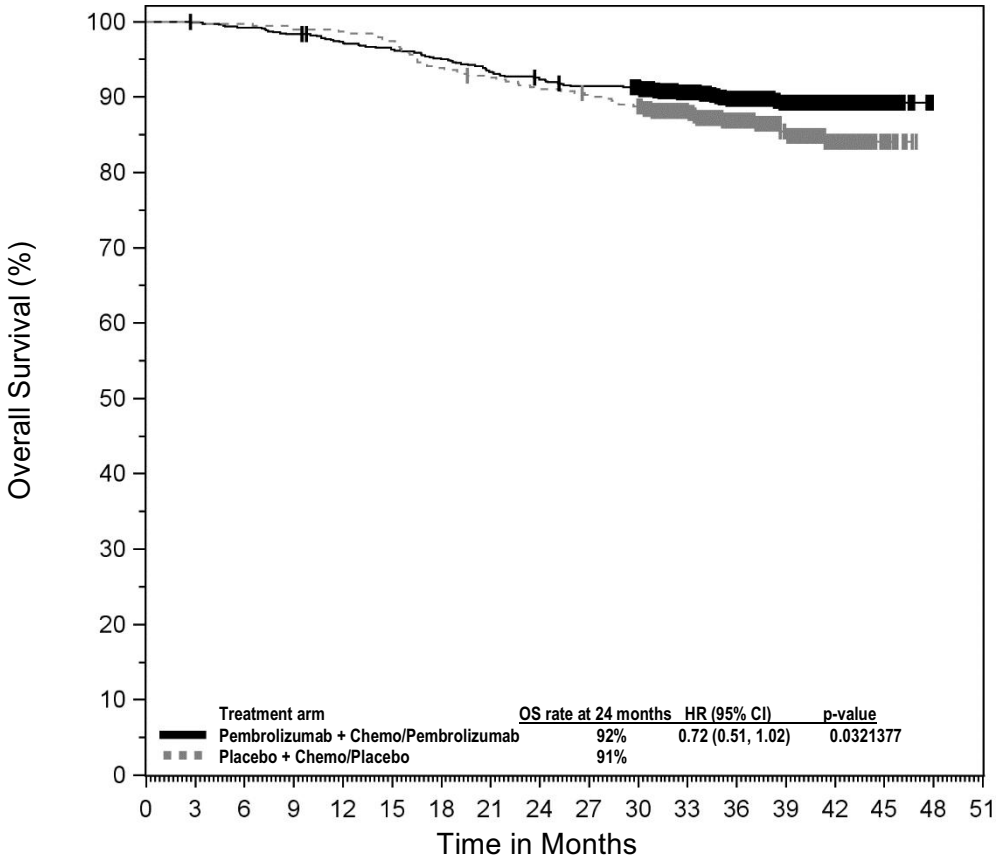
Figure 36: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-522 (intent to treat population)



Number at Risk

Pembrolizumab + Chemo/Pembrolizumab:	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + Chemo/Placebo:	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Figure 37: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-522 (intent to treat population)



KEYNOTE-355: Controlled study of combination therapy in TNBC patients previously untreated for metastatic disease

The efficacy of pembrolizumab in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a randomised, double-blind, multicentre, placebo-controlled study. Key eligibility criteria were locally recurrent unresectable or metastatic TNBC, regardless of tumour PD-L1 expression, not previously treated with chemotherapy in the advanced setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel vs. gemcitabine and carboplatin), tumour PD-L1 expression (CPS $\geq$ 1 vs. CPS < 1), and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no). Patients were randomised (2:1) to one of the following treatment arms via intravenous infusion:

- Pembrolizumab 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1 000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.
- Placebo on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every

28 days, or gemcitabine 1 000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Treatment with pembrolizumab or placebo, both in combination with chemotherapy, continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Chemotherapy could continue per standard of care. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumour status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter.

Among the 847 patients randomised in KEYNOTE-355, 636 (75%) had tumours that expressed PD-L1 with a CPS ≥ 1 and 323 (38%) had tumour PD-L1 expression CPS ≥ 10 based on the PD-L1 IHC 22C3 pharmDx^{TM} Kit. The baseline characteristics of the 323 patients with tumour PD-L1 expression CPS ≥ 10 included: median age of 53 years (range: 22 to 83); 20% age 65 or older; 100% female; 69% White, 20% Asian, and 5% Black; ECOG performance status of 0 (61%) and 1 (39%); 67% were post-menopausal status; 3% had a history of brain metastases; and 20% had disease-free interval of < 12 months.

The dual primary efficacy outcome measures were PFS as assessed by BICR using RECIST 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration as assessed by BICR using RECIST 1.1. The study demonstrated a statistically significant improvement in PFS at its pre-specified interim analysis (HR 0.65; 95% CI 0.49, 0.86; p-Value 0.0012) and OS at final analysis for patients with tumour PD-L1 expression CPS ≥ 10 randomised to the pembrolizumab in combination with chemotherapy arm compared with placebo in combination with chemotherapy. Table 43 summarises key efficacy measures and Figures 38 and 39 show the Kaplan-Meier curves for PFS and OS based on the final analysis with a median follow-up time of 20.2 months (range: 0.3 to 53.1 months) for patients with tumour PD-L1 expression CPS ≥ 10.

Table 43: Efficacy results in KEYNOTE-355 patients with CPS ≥ 10

Endpoint	Pembrolizumab with chemotherapy* n=220	Placebo with chemotherapy* n=103
PFS†		
Number (%) of patients with event	144 (65%)	81 (79%)
Hazard ratio‡ (95% CI)	0.66 (0.50, 0.88)	
p-Value§	0.0018	
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
OS		
Number (%) of patients with event	155 (70%)	84 (82%)
Hazard ratio‡ (95% CI)	0.73 (0.55, 0.95)	
p-Value¶	0.0093	
Median in months (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
Objective response rate†		
ORR % (95% CI)	53% (46, 59)	41% (31, 51)
Complete response	17%	14%
Partial response	35%	27%
Response duration†		
Median in months (range)	12.8 (1.6+, 45.9+)	7.3 (1.5, 46.6+)
% with duration ≥ 6 months#	82%	60%
% with duration ≥ 12 months#	56%	38%

* Chemotherapy: paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin

† Assessed by BICR using RECIST 1.1

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

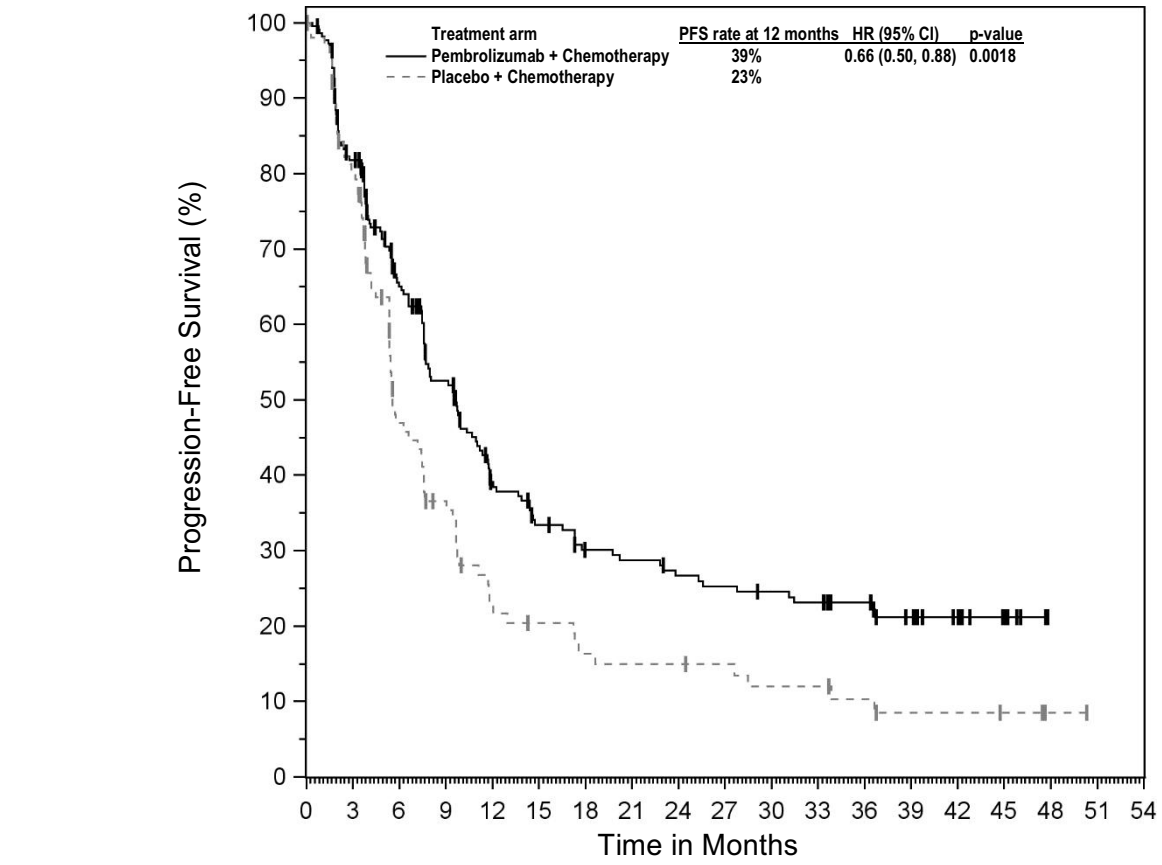
§ Nominal p-Value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no). At the pre-specified interim analysis of PFS (median follow-up time of 19.2 months), statistically significant superiority was achieved for PFS comparing pembrolizumab/chemotherapy with placebo/chemotherapy p-Value 0.0012.

¶ One-sided p-Value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no). OS results met the pre-specified efficacy boundary of 0.0113 for statistical significance.

From product-limit (Kaplan-Meier) method for censored data

\+ Denotes there is no progressive disease by the time of last disease assessment

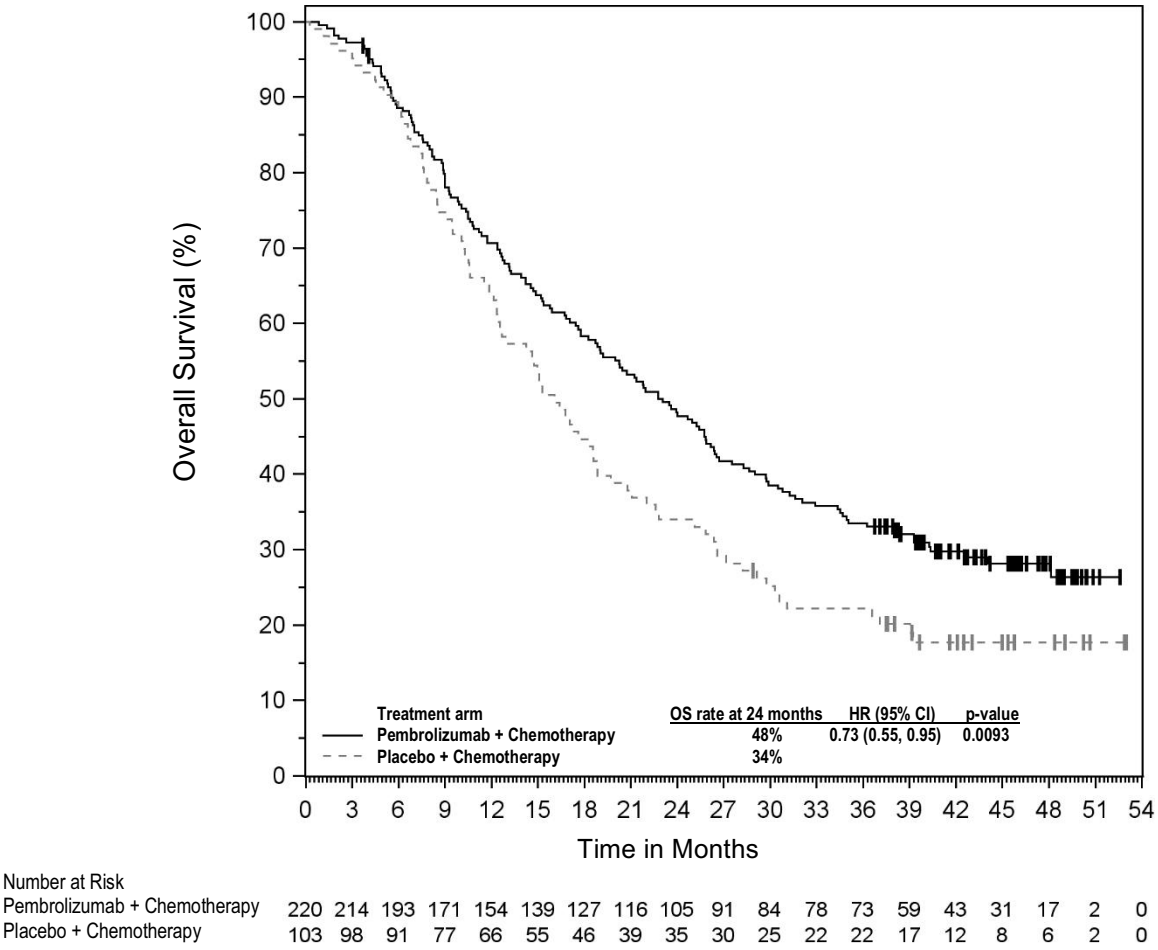
Figure 38: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-355 patients with PD-L1 expression (CPS ≥ 10)



Number at Risk

Pembrolizumab + Chemotherapy	220	173	122	95	63	52	44	42	38	36	34	32	27	19	13	6	0	0	0
Placebo + Chemotherapy	103	80	41	30	18	15	12	11	11	10	8	8	6	4	4	3	1	0	0

Figure 39: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-355 patients with PD-L1 expression (CPS ≥ 10)



Endometrial carcinoma

KEYNOTE-775: Controlled study of combination therapy in advanced EC patients previously treated with systemic chemotherapy

The efficacy of pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-775, a randomised, multicentre, open-label, active-controlled study conducted in patients with advanced EC who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Participants may have received up to 2 platinum-containing therapies in total, as long as one was given in the neoadjuvant or adjuvant treatment setting. The study excluded patients with endometrial sarcoma, carcinosarcoma, pre-existing Grade ≥ 3 fistula, uncontrolled BP (> 150/90 mmHg), significant cardiovascular impairment or event within previous 12 months, or patients who had active autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by MMR status (dMMR or pMMR [mismatch repair proficient]) using a validated IHC test. The pMMR stratum was further stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomised (1:1) to one of the following treatment arms:

- pembrolizumab 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- investigator's choice consisting of either doxorubicin 60 mg/m^2 every 3 weeks, or paclitaxel 80 mg/m^2 weekly, 3 weeks on/1 week off.

Treatment with pembrolizumab and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months.

Administration of study treatment was permitted beyond RECIST-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. A total of 121/411 (29%) of the pembrolizumab and lenvatinib-treated patients received continued study therapy beyond RECIST-defined disease progression. The median duration of the post-progression therapy was 2.8 months. Assessment of tumour status was performed every 8 weeks.

A total of 827 patients were enrolled and randomised to pembrolizumab in combination with lenvatinib (n=411) or investigator's choice of doxorubicin (n=306) or paclitaxel (n=110). The baseline characteristics of these patients were: median age of 65 years (range: 30 to 86), 50% age 65 or older; 61% White, 21% Asian, and 4% Black; ECOG PS of 0 (59%) or 1 (41%), and 84% with pMMR tumour status and 16% with dMMR tumour status. The histologic subtypes were endometrioid carcinoma (60%), serous (26%), clear cell carcinoma (6%), mixed (5%), and other (3%). All 827 of these patients received prior systemic therapy for EC: 69% had one, 28% had two, and 3% had three or more prior systemic therapies. 37% of patients received only prior neoadjuvant or adjuvant therapy.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. At the pre-specified interim analysis, with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), the study demonstrated a statistically significant improvement in OS and PFS. The pre-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without multiplicity adjustment. Efficacy results by MMR subgroups were consistent with overall study results. PFS, ORR and response duration results at the interim analysis and OS results at final analysis are summarised in Table 44. Kaplan-Meier curves for final OS and interim PFS analyses are shown in Figures 40 and 41, respectively.

Table 44: Efficacy results in KEYNOTE-775

Endpoint	Pembrolizumab 200 mg every 3 weeks Lenvatinib n=411	Chemotherapy* n=416
OS		
Number (%) of patients with event	276 (67%)	329 (79%)
Median in months (95% CI)	18.7 (15.6, 21.3)	11.9 (10.7, 13.3)
Hazard ratio† (95% CI)	0.65 (0.55, 0.77)	
p-Value[Þ]	< 0.0001	
PFS[ß]		
Number (%) of patients with event	281 (68%)	286 (69%)
Median in months (95% CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
Hazard ratio† (95% CI)	0.56 (0.47, 0.66)	
p-Value‡	< 0.0001	
Objective response rate[ß]		
ORR§ % (95% CI)	32% (27, 37)	15% (11, 18)
Complete response	7%	3%
Partial response	25%	12%
p-Value¶	< 0.0001	
Response duration[ß]		
Median in months# (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

* Doxorubicin or Paclitaxel

† Based on the stratified Cox regression model

Þ One-sided nominal p-Value for final analysis based on stratified log-rank test. At the pre-specified interim analysis of OS with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), statistically significant superiority was achieved for OS comparing the combination of pembrolizumab and lenvatinib with chemotherapy (HR: 0.62 [95% CI: 0.51, 0.75] p-Value < 0.0001)

ß At pre-specified interim analysis

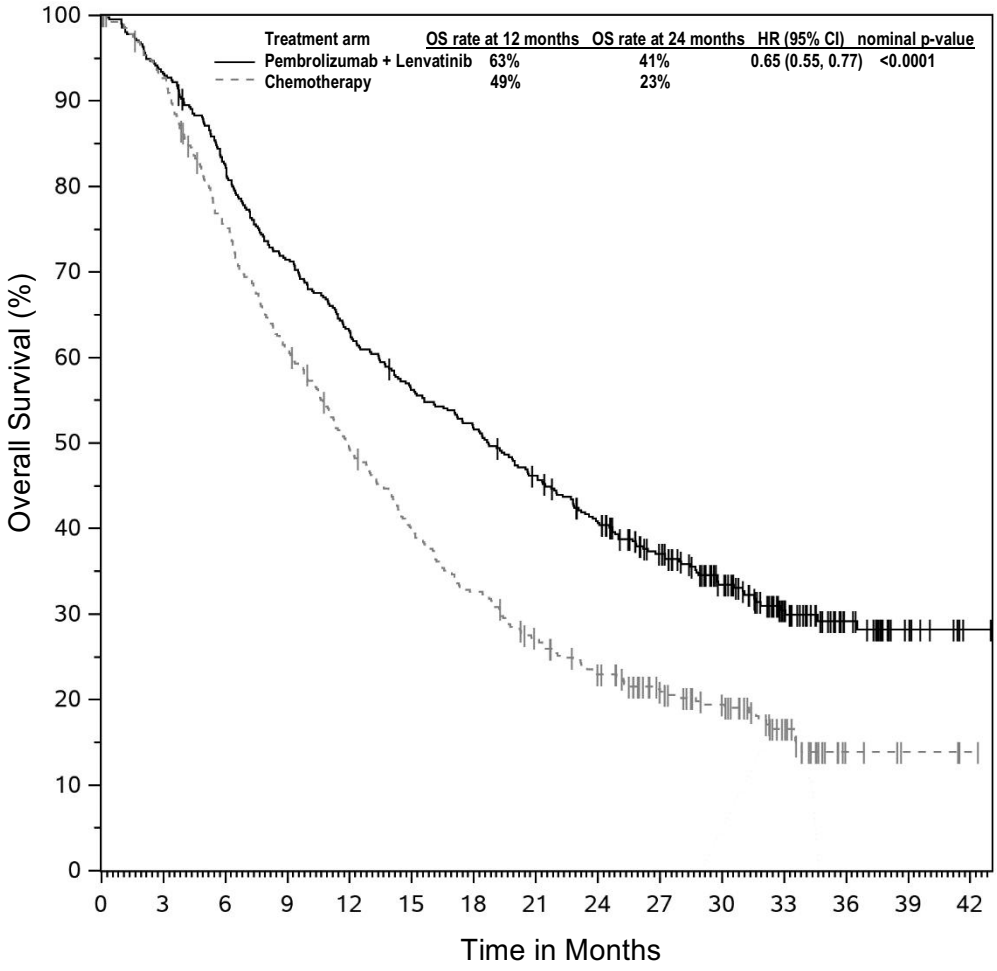
‡ One-sided p-Value based on stratified log-rank test

§ Response: Best objective response as confirmed complete response or partial response

¶ Based on Miettinen and Nurminen method stratified by MMR Status, ECOG performance status, geographic region, and history of pelvic radiation

Based on Kaplan-Meier estimation

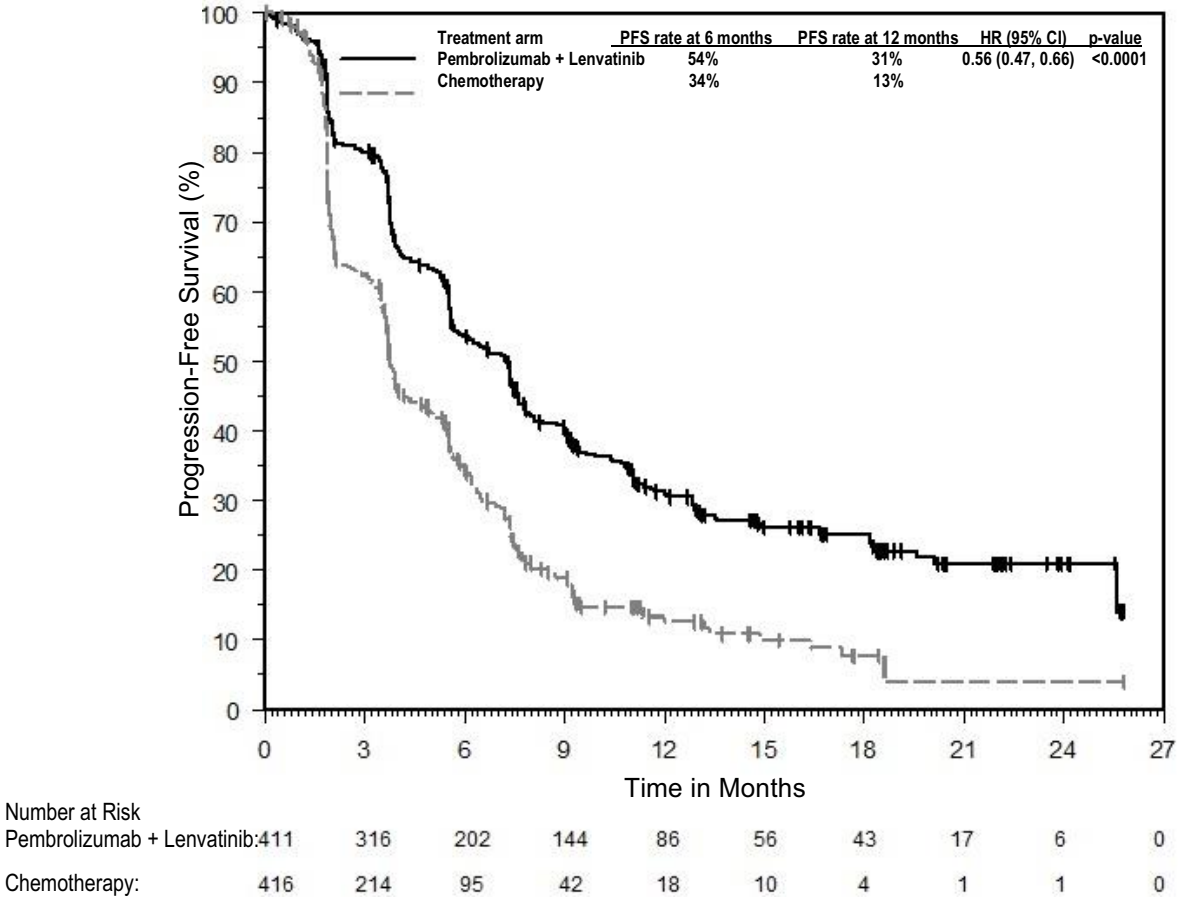
Figure 40: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-775 (intent to treat population)



Number at Risk

Pembrolizumab + Lenvatinib	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

Figure 41: Kaplan-Meier curve for progression free-survival by treatment arm in KEYNOTE-775 (intent to treat population)



Cervical cancer

KEYNOTE-826: Controlled study of combination therapy in patients with persistent, recurrent, or metastatic cervical cancer

The efficacy of pembrolizumab in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitising agent. Patients were enrolled regardless of tumour PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS < 1 vs. CPS 1 to < 10 vs. CPS ≥ 10). Patients were randomised (1:1) to one of the two treatment groups:

- Treatment Group 1: Pembrolizumab 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomisation:

1. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2
2. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to

randomisation. Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter.

Of the 617 enrolled patients, 548 patients (89%) had tumours expressing PD-L1with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx™ Kit. Among these 548 enrolled patients with tumours expressing PD-L1, 273 patients were randomised to pembrolizumab in combination with chemotherapy with or without bevacizumab, and 275 patients were randomised to placebo in combination with chemotherapy with or without bevacizumab. The baseline characteristics of these 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, and 1% Black; 37% Hispanic or Latino; 56% and 43% ECOG performance status of 0 or 1, respectively; 63% received bevacizumab as study treatment; 21% with adenocarcinoma and 5% with adenosquamous histology; for patients with persistent or recurrent disease with or without distant metastases, 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

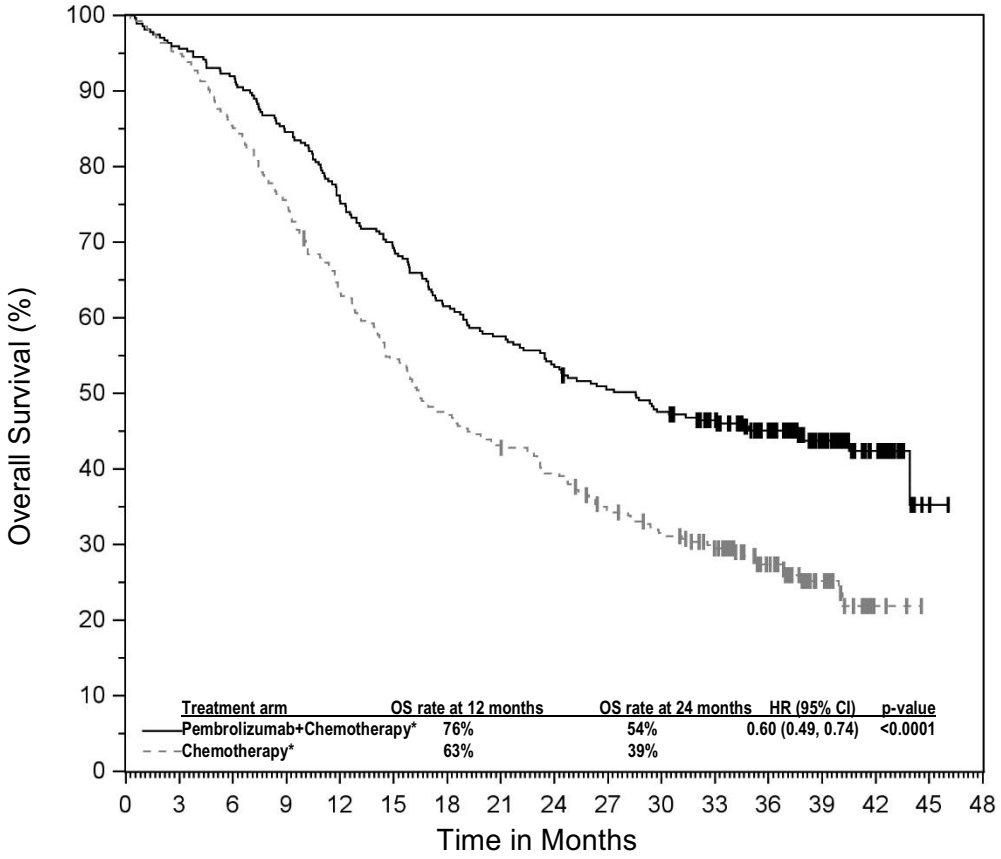
The primary efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and duration of response, according to RECIST v1.1, as assessed by investigator. At a pre-specified interim analysis, the study demonstrated statistically significant improvements in OS (HR 0.64; 95% CI 0.50, 0.81; p-Value = 0.0001) and PFS (HR 0.62; 95% CI 0.50, 0.77; p-Value < 0.0001) for patients whose tumours expressed PD-L1 with a CPS ≥ 1 randomised to pembrolizumab in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab. The study also demonstrated statistically significant improvements in OS and PFS in the overall population. Table 45 summarises key efficacy measures for patients whose tumours expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-826 at the final analysis with a median duration of follow-up of 21.3 months. The Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 42 and 43.

Table 45: Efficacy results in KEYNOTE-826 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab 200 mg every 3 weeks plus Chemotherapy* with or without bevacizumab n=273	Placebo plus Chemotherapy* with or without bevacizumab n=275
OS		
Number (%) of patients with event	153 (56%)	201 (73%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
p-Value‡	< 0.0001	
PFS		
Number (%) of patients with event	171 (63%)	220 (80%)
Median in months (95% CI)	10.5 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio† (95% CI)	0.58 (0.47, 0.71)	
p-Value‡	< 0.0001	
Objective response rate		
ORR¶ % (95% CI)	69% (63, 74)	51% (45, 57)
Complete response	26%	15%
Partial response	43%	36%
Response duration		
Median in months (range)	19.2 (1.3+, 40.9+)	10.4 (1.5+, 40.7+)
% with duration ≥ 12 months#	56	45
% with duration ≥ 24 months#	48	30

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ Nominal p-Value based on stratified log-rank test
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Kaplan-Meier estimation

Figure 42: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)

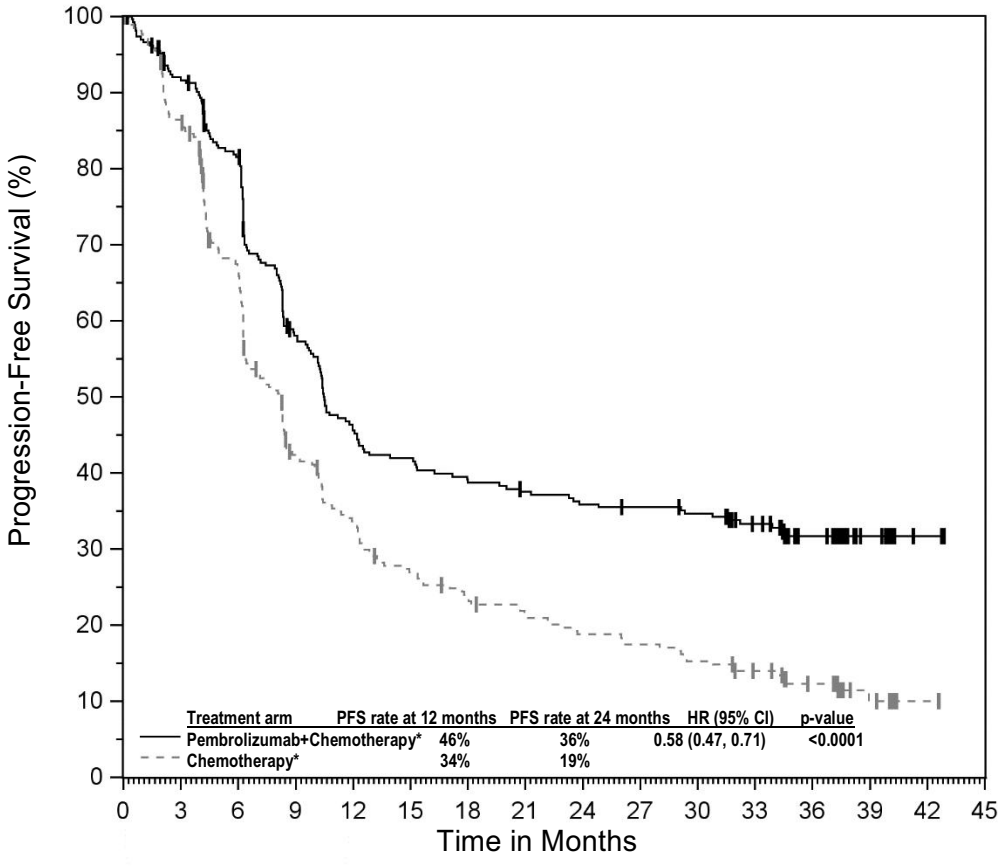


Number at Risk

Pembrolizumab+Chemotherapy*	273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
Chemotherapy*	275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Figure 43: Kaplan-Meier curve for progression free survival by treatment arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk

Pembrolizumab+Chemotherapy*	273	238	208	144	113	104	97	92	88	86	83	70	46	25	6	0
Chemotherapy*	275	229	170	103	81	64	55	49	43	40	35	28	18	7	2	0

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

KEYNOTE-811: Controlled study of combination therapy in locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma patients naïve to treatment

The efficacy of pembrolizumab in combination with trastuzumab plus fluoropyrimidine and platinum-containing chemotherapy was investigated in KEYNOTE-811, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 698 patients with HER2-positive advanced gastric or GEJ adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

Randomisation was stratified by PD-L1 expression (CPS ≥ 1 or < 1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia or Rest of the World). Patients were randomised (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week treatment cycle:

- Pembrolizumab 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX). Pembrolizumab was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.

- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX). Placebo was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.

Treatment with pembrolizumab, trastuzumab and chemotherapy or placebo, trastuzumab and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Assessment of tumour status was performed every 6 weeks.

Among the 698 patients randomised in KEYNOTE-811, 594 (85%) had tumours that expressed PD-L1 with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx^{TM} kit. The baseline characteristics of the 594 patients with tumour PD-L1 expression CPS ≥ 1 included: median age of 63 years (range: 19 to 85), 43% age 65 or older; 80% male; 63% White, 33% Asian, and 0.7 % Black; 42% ECOG PS of 0 and 58% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (stage IV) and 2% had locally advanced unresectable disease. Ninety-five percent (n=562) had tumours that were not MSI H, 1% (n=8) had tumours that were MSI H, and in 4% (n=24) the status was not known. Eighty-five percent of patients received CAPOX.

The primary efficacy outcome measures were PFS based on BICR using RECIST 1.1, and OS. Secondary efficacy outcome measures included ORR and DoR based on BICR using RECIST 1.1. At the second interim analysis in the overall population, the study demonstrated a statistically significant improvement in PFS (HR 0.72; 95% CI 0.60, 0.87; p-Value 0.0002) for patients randomised to the pembrolizumab arm in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. At this interim analysis, there was no statistically significant difference with respect to OS. The median follow-up time was 15.4 months (range: 0.3 to 41.6 months). At the first interim analysis conducted on the first 264 patients randomised in the overall population (133 patients in the pembrolizumab arm and 131 in the placebo arm), a statistically significant improvement was observed in ORR (74.4% vs. 51.9%, representing a 22.7% difference in ORR, [95%CI: 11.2, 33.7]; p-Value 0.00006).

Table 46 summarises key efficacy results at the second interim analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 and Figures 44 and 45 show the Kaplan-Meier curves for PFS and OS.

Table 46: Efficacy results for KEYNOTE-811 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab Trastuzumab and Chemotherapy n=298	Placebo Trastuzumab and Chemotherapy n=296
PFS		
Number (%) of patients with event	199 (67%)	215 (73%)
Median in months (95% CI)	10.8 (8.5, 12.5)	7.2 (6.8, 8.4)
Hazard ratio* (95% CI)	0.7 (0.58, 0.85)	
p-Value†	0.0001	
OS		
Number (%) of patients with event	167 (56%)	183 (62%)
Median in months (95% CI)	20.5 (18.2, 24.3)	15.6 (13.5, 18.6)
Hazard ratio* (95% CI)	0.79 (0.64, 0.98)	
p-Value†	0.0143	
Objective response rate		
ORR‡ % (95% CI)	73% (67.7, 78.1)	58% (52.6, 64.1)
Complete response	14%	10%
Partial response	59%	49%
p-Value#	0.00008	
Response duration		
Median in months (range)	11.3 (1.1+, 40.1+)	9.5 (1.4+, 38.3+)
% with duration ≥ 6 months¶	75%	67%
% with duration ≥ 12 months¶	49%	41%

* Based on unstratified Cox proportional hazard model

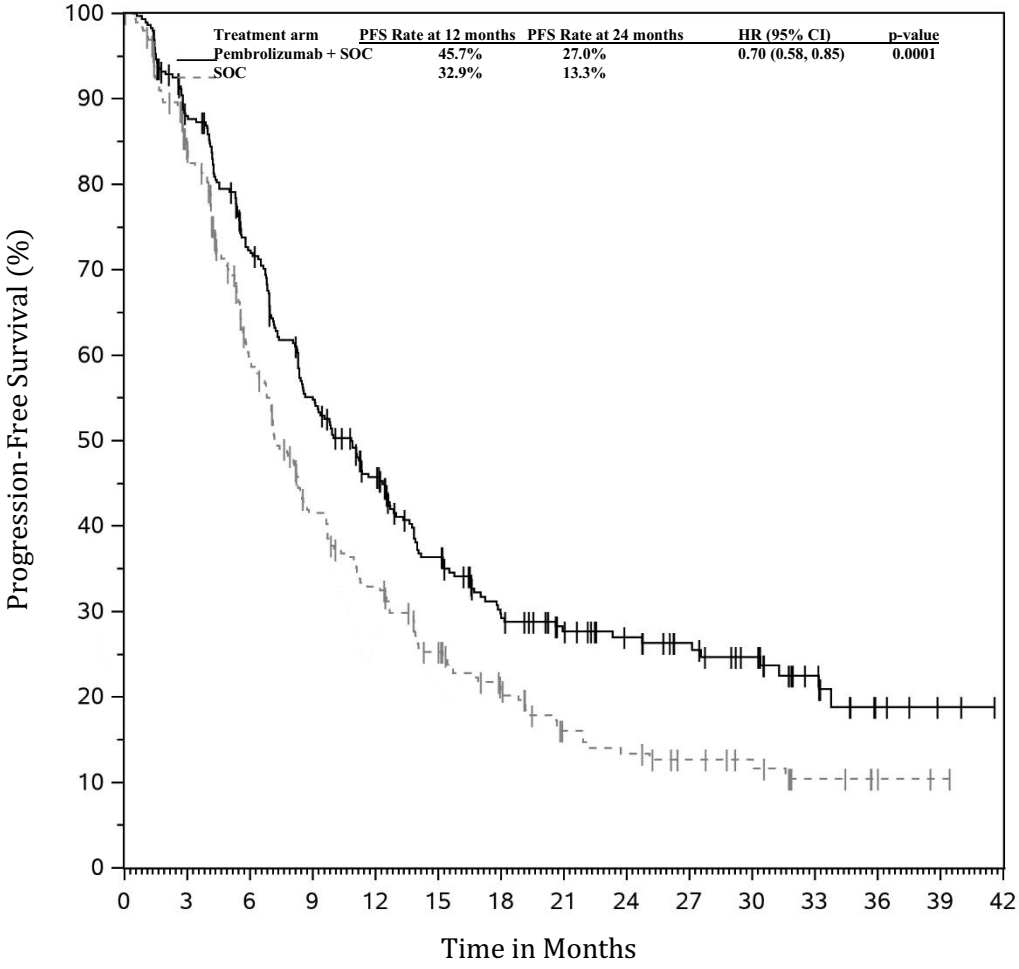
† Nominal p-value based on unstratified log-rank test; no formal test was performed in patients with PD-L1 expression (CPS ≥ 1).

‡ Response: Best objective response as confirmed complete response or partial response

Nominal p-value based on unstratified Miettinen and Nurminen method; no formal test was performed in patients with PD-L1 expression (CPS ≥ 1).

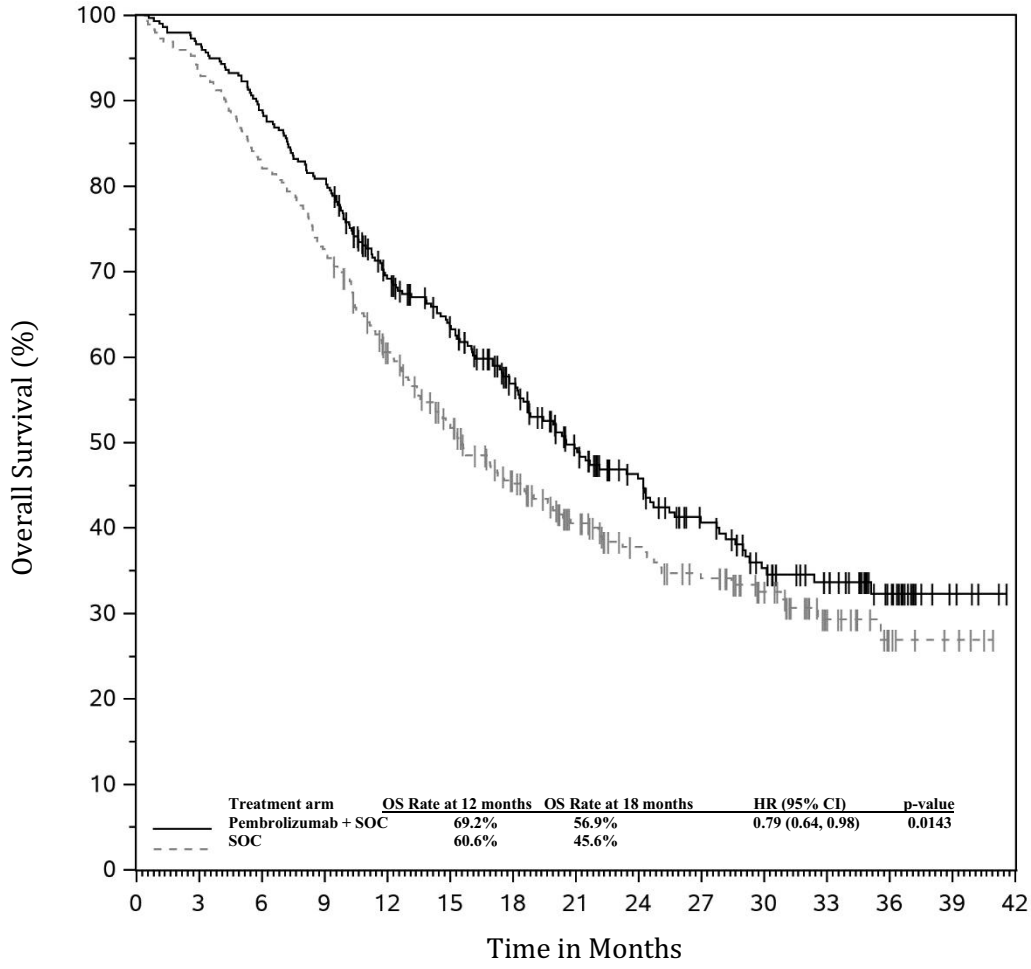
¶ Based on Kaplan-Meier estimation

Figure 44: Kaplan-Meier curve for progression free survival by treatment arm in KEYNOTE-811 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk															
Pembrolizumab + SOC	298	250	200	150	116	84	61	48	40	33	26	14	5	2	0
SOC	296	231	150	98	76	54	38	24	20	15	12	6	3	1	0

Figure 45: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-811 patients with PD-L1 expression (CPS ≥ 1)



KEYNOTE-859: Controlled study of combination therapy in locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma patients naïve to treatment

The efficacy of pembrolizumab in combination with fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-859, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 1 579 patients with HER2-negative advanced gastric or GEJ adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Prior neoadjuvant and/or adjuvant therapy was allowed if it was completed at least 6 months prior to randomisation. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or patients who had received prior treatment with immune checkpoint inhibitors were ineligible.

Randomisation was stratified by PD-L1 expression (CPS ≥ 1 or < 1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia or Rest of the World).

Patients were randomised (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week treatment cycle:

- Pembrolizumab 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. Duration

of cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. Pembrolizumab was administered prior to chemotherapy on Day 1 of each cycle.

- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. Duration of cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. Placebo was administered prior to chemotherapy on Day 1 of each cycle.

Treatment with pembrolizumab and chemotherapy or placebo and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Assessment of tumour status was performed every 6 weeks.

Among the 1 579 patients in KEYNOTE-859, 1 235 (78%) had tumours that expressed PD-L1 with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx^{TM} kit. The baseline characteristics of the 1 235 patients with tumour PD-L1 expression CPS ≥ 1 included: median age of 62 years (range: 24 to 86), 40% age 65 or older; 70.4% male; 55.5% White; 33.1% Asian; 36.5% ECOG PS of 0 and 63.5% ECOG PS of 1. Ninety-six percent of patients had metastatic disease (stage IV) and 4% had locally advanced unresectable disease. Five percent (n=66) had tumours that were MSI-H. Eighty-six percent of patients received CAPOX.

The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DOR as assessed by BICR using RECIST 1.1.

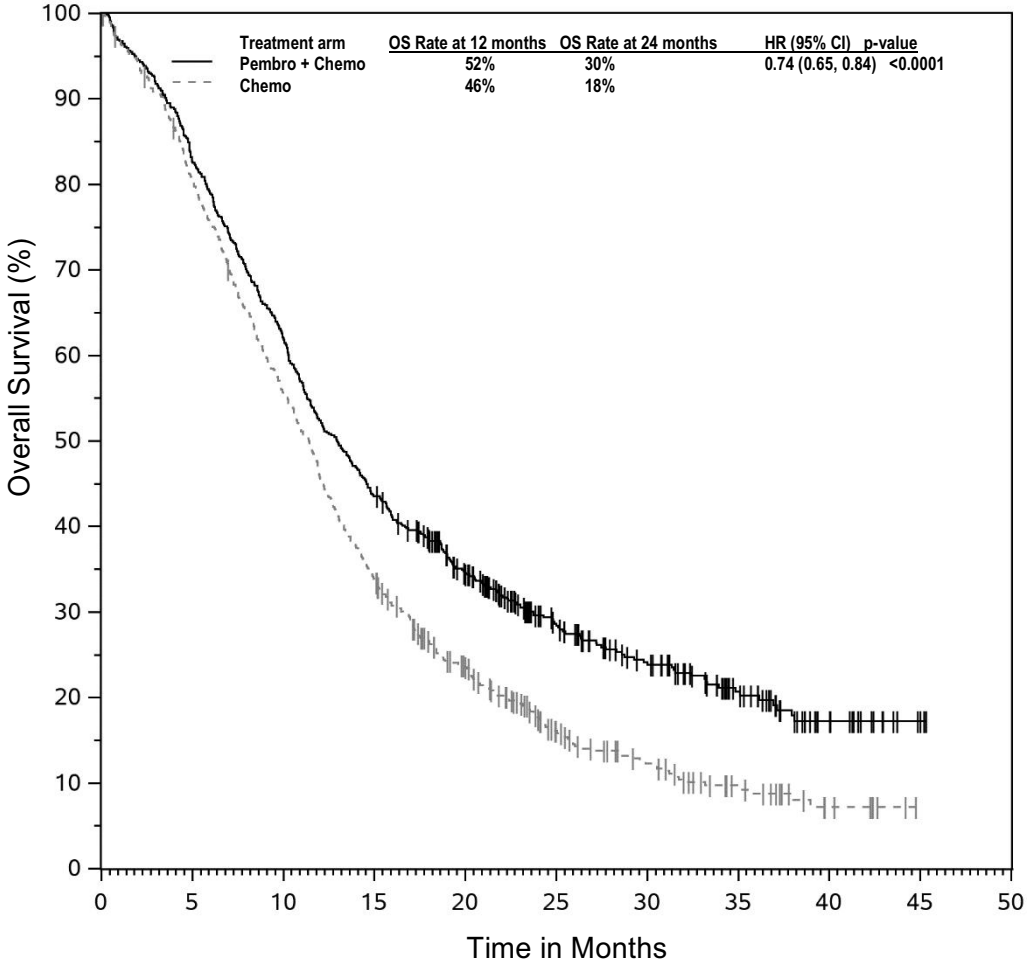
The study demonstrated a statistically significant improvement in OS (HR 0.78; 95% CI 0.70, 0.87; p-Value < 0.0001), PFS (HR 0.76; 95% CI 0.67, 0.85; p-Value < 0.0001) and ORR (51% [95% CI 47.7, 54.8] vs 42% [95% CI 38.5, 45.5]; p-Value 0.00009) in patients randomised to pembrolizumab in combination with chemotherapy compared with placebo in combination with chemotherapy in the overall population. The median follow-up time was 12 months (range: 0.1 to 45.9 months). Table 47 summarises key efficacy results for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 and Figures 46 and 47 show the Kaplan-Meier curves for OS and PFS.

Table 47: Efficacy results in KEYNOTE-859 for patients with PD L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab Fluoropyrimidine and Platinum Chemotherapy n=618	Placebo Fluoropyrimidine and Platinum Chemotherapy n=617
OS		
Number (%) of patients with event	464 (75%)	526 (85%)
Median in months* (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)
Hazard ratio† (95% CI)	0.74 (0.65, 0.84)	
p-Value‡	< 0.0001	
PFS		
Number (%) of patients with event	443 (72%)	483 (78%)
Median in months* (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)
Hazard ratio† (95% CI)	0.72 (0.63, 0.82)	
p-Value‡	< 0.0001	
Objective response rate		
ORR§ (95% CI)	52% (48.1, 56.1)	43% (38.7, 46.6)
Complete response	10%	6%
Partial response	42%	37%
p-Value¶	0.00041	
Response duration		
Median in months* (range)	8.3 (1.2+, 41.5+)	5.6 (1.3+, 34.2+)
% with duration ≥ 12 months*	41%	26%

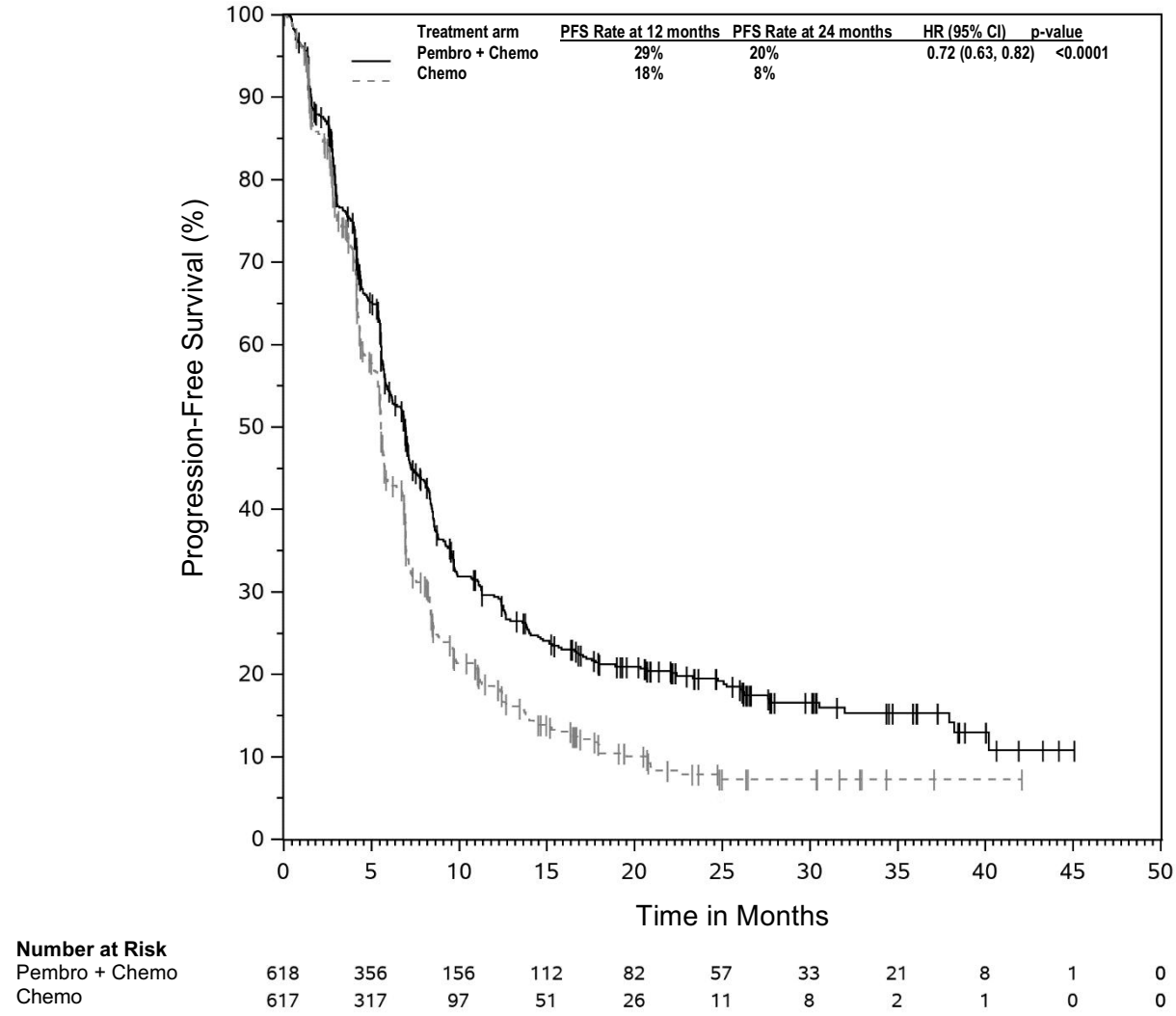
* Based on Kaplan-Meier estimation
† Based on the stratified Cox proportional hazard model
‡ One sided p-Value based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ One sided p-Value based on stratified Miettinen and Nurminen method

Figure 46: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-859 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk											
Pembro + Chemo	618	511	383	269	192	121	81	46	17	3	0
Chemo	617	493	339	206	126	66	41	20	7	0	0

Figure 47: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-859 patients with PD-L1 expression (CPS ≥ 1)



An analysis was performed in KEYNOTE-859 in patients whose tumours expressed PD-L1 with a CPS ≥ 1 to < 10 or CPS ≥ 10 in both arms (see Table 48).

Table 48: Efficacy results by PD-L1 expression in KEYNOTE-859

Endpoint	Pembrolizumab combination therapy n=337	Chemotherapy n=345	Pembrolizumab combination therapy n=279	Chemotherapy n=272
	CPS ≥ 1 to < 10		CPS ≥ 10	
OS HR (95% CI)	0.83 (0.70, 0.98)*		0.65 (0.53, 0.79)†	
PFS HR (95% CI)	0.83 (0.70, 0.99)*		0.62 (0.51, 0.76)†	
ORR§ (95% CI)	45% (39.7, 50.6)	42% (37.0, 47.7)	61% (54.6, 66.3)	43% (37.1, 49.1)

* Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on unstratified Cox proportional hazard model

† Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on stratified Cox proportional hazard model

§ Response: Best objective response as confirmed complete response or partial response

Biliary tract carcinoma

KEYNOTE-966: Controlled study of combination therapy in patients with locally advanced unresectable or metastatic BTC

The efficacy of pembrolizumab in combination with gemcitabine and cisplatin was investigated in KEYNOTE-966, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 1 069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients were enrolled regardless of tumour PD-L1 expression. Patients must have had acceptable serum bilirubin levels (≤ 1.5 x ULN or direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 × ULN) and any clinically significant biliary obstruction had to be resolved before randomisation. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by geographic region (Asia vs. non-Asia), locally advanced versus metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomised (1:1) to one of the two treatment groups:

- Pembrolizumab 200 mg on Day 1 plus gemcitabine 1 000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks
- Placebo on Day 1 plus gemcitabine 1 000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks

All study medications were administered via intravenous infusion. Treatment was continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment was continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be administered for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 8 cycles. Assessment of tumour status was performed at baseline and then every 6 weeks through 54 weeks followed by every 12 weeks thereafter.

The study population characteristics were median age of 64 years (range: 23 to 85), 47% age 65 or older; 52% male; 49% White, 46% Asian; 46% ECOG PS of 0 and 54% ECOG PS of 1; 31% of patients had a history of hepatitis B infection, and 3% had a history of hepatitis C infection.

The primary efficacy outcome measure was OS and the secondary efficacy measures were PFS, ORR and DOR as assessed by BICR using RECIST 1.1. The study demonstrated a statistically significant improvement in OS at final analysis for patients randomised to pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy. Table 49 summarises key efficacy measures and Figures 48 and 49 show the Kaplan-Meier curves for PFS and OS based on the final analysis with a median follow-up time of 11.6 months (range: 0.2 to 37.5 months).

Table 49: Efficacy results in KEYNOTE-966

Endpoint	Pembrolizumab 200 mg every 3 weeks with gemcitabine/cisplatin n=533	Placebo with gemcitabine/cisplatin n=536
OS		
Number (%) of patients with event	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio* (95% CI)	0.83 (0.72, 0.95)	
p-Value†	0.0034	
PFS		
Number (%) of patients with event	428 (80%)	448 (84%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (4.9, 6.5)
Hazard ratio* (95% CI)	0.87 (0.76, 0.99)	
p-Value‡	0.0171	
Objective response rate		
ORR% (95% CI)	29.3% (25.4, 33.3)	28.4% (24.6, 32.4)
Complete response	2.6%	1.7%
Partial response	26.6%	26.7%
p-Value$^{\alpha}$	0.3610	
Response duration§,¶		
Median in months (range)	8.3 (1.2+, 33.0+)	6.8 (1.1+, 30.0+)
% with duration ≥ 6 months¶	65%	55%
% with duration ≥ 12 months¶	38%	27%

* Based on the stratified Cox proportional hazard model

† One-sided p-Value based on a stratified log-rank test. The OS result met the pre-specified one-sided significance level of 0.0200

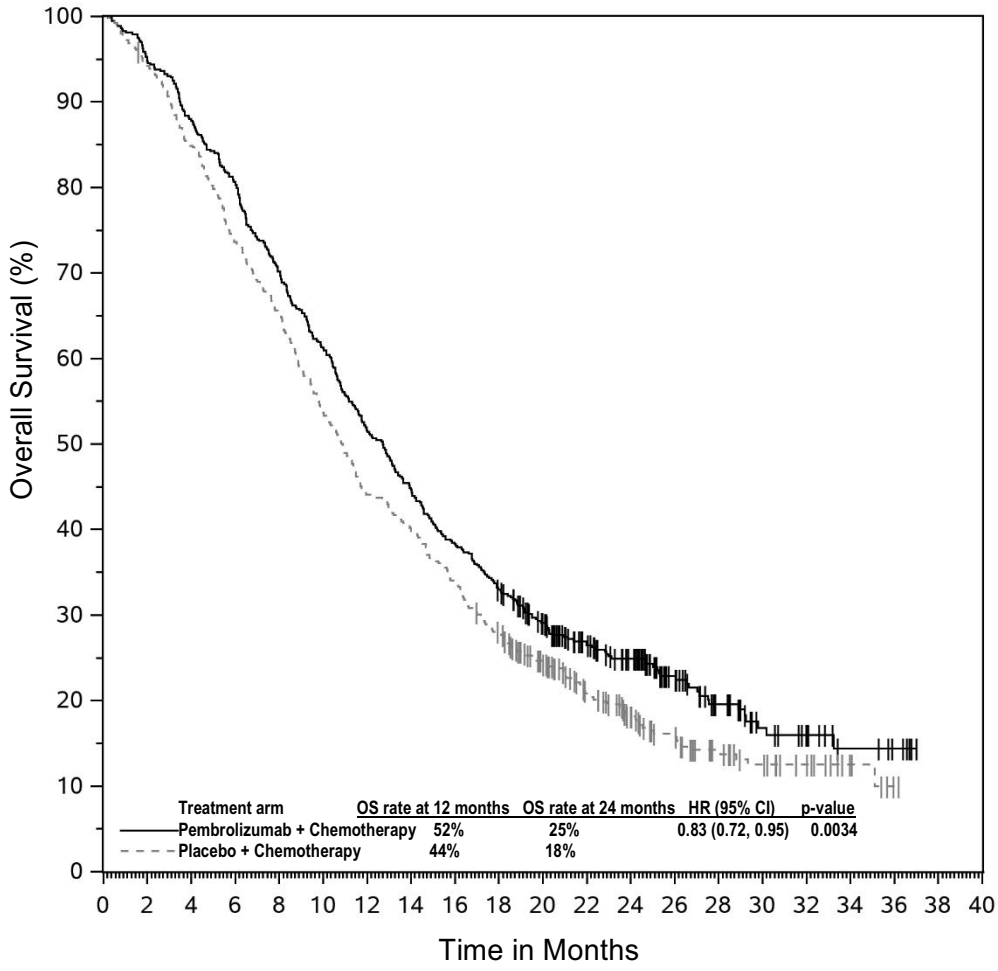
‡ One-sided p-Value based on stratified log-rank test. The PFS result did not meet the pre-specified one-sided significance level of 0.0125

$^{\alpha}$ One-sided p-Value based on the stratified Miettinen and Nurminen method. The ORR result did not meet the pre-specified one-sided significance level of 0.0125

§ Based on patients with objective response that is confirmed complete response or partial response

¶ Based on Kaplan-Meier estimate

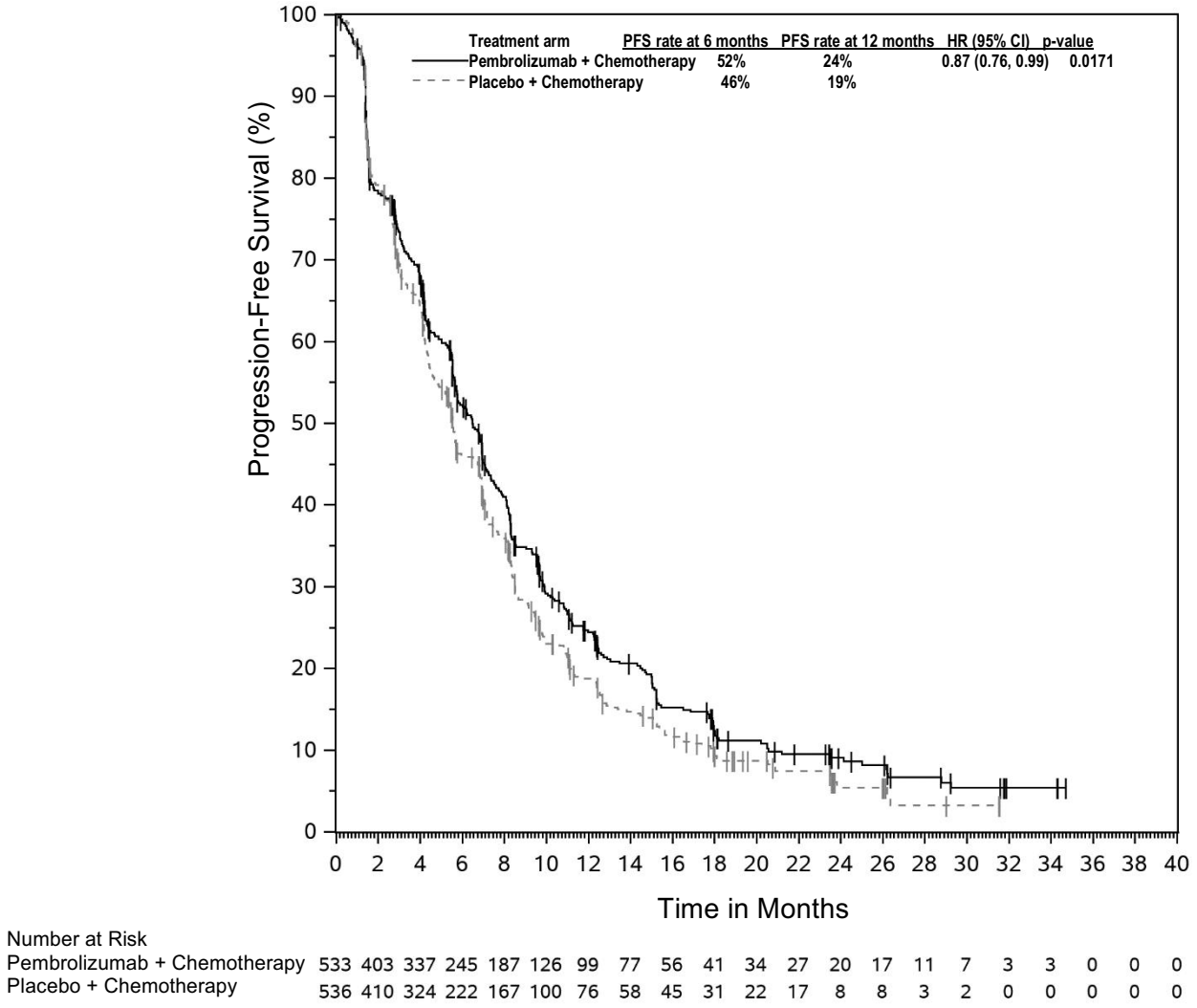
Figure 48: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-966 (intent to treat population)



Number at Risk

Pembrolizumab + Chemotherapy	533	505	469	430	374	326	275	238	204	175	142	108	88	56	35	21	16	8	5	0	0
Placebo + Chemotherapy	536	504	454	394	349	287	236	213	181	148	115	81	59	43	28	20	14	7	1	0	0

Figure 49: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-966 (intent to treat population)



Elderly population

No overall differences in safety were observed in patients ≥ 75 years of age compared to younger patients receiving pembrolizumab monotherapy. Based on limited safety data from patients ≥ 75 years of age, when administrated in combination with chemotherapy, pembrolizumab showed less tolerability in patients ≥ 75 years of age compared to younger patients. For efficacy data in patients ≥ 75 years of age please refer to the relevant section of each indication.

Paediatric population

In KEYNOTE-051, 161 paediatric patients (62 children aged 9 months to less than 12 years and 99 adolescents aged 12 years to 17 years) with advanced melanoma or PD-L1 positive advanced, relapsed, or refractory solid tumours or lymphoma were administered pembrolizumab 2 mg/kg bw every 3 weeks. All patients received pembrolizumab for a median of 4 doses (range: 1-35 doses), with 138 patients (85.7%) receiving pembrolizumab for 2 doses or more. Participants were enrolled across 28 tumour types by primary diagnosis. The most common tumour types by histology were Hodgkin lymphoma (13.7%), glioblastoma multiforme (9.3%), neuroblastoma (6.2%), osteosarcoma (6.2%) and melanoma (5.6%). Of the 161 patients, 137 were enrolled with solid tumours, 22 with Hodgkin lymphoma, and 2 with other lymphomas. In patients with solid tumours and other lymphomas, the ORR was 5.8%, no patient had a complete response and 8 patients (5.8%) had a partial response. In the Hodgkin lymphoma population (n=22), in patients aged 11 years to 17 years, the baseline characteristics were median age 15 years; 64% male; 68% White; 77% had a Lansky/Karnofsky scale 90-100 and 23% had scale 70-80. Eighty-six percent had two or more prior lines of therapy and 64%

had Stage 3 or higher. In these paediatric patients with cHL, the ORR assessed by BICR according to the IWG 2007 criteria was 54.5%, 1 patient (4.5%) had a complete response and 11 patients (50.0%) had a partial response, and the ORR assessed by the Lugano 2014 criteria was 63.6%, 4 patients (18.2%) had a complete response and 10 patients (45.5%) had a partial response. Data from clinical trials in adolescent melanoma patients is very limited and extrapolation from adult data has been used to establish efficacy. Among the 5 adolescent participants with advanced melanoma treated on KEYNOTE-051, no patient had a complete or a partial response, and 1 patient had stable disease.

The European Medicines Agency has deferred the obligation to submit the results of studies with pembrolizumab in one or more subsets of the paediatric population in treatment of Hodgkin lymphoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2 993 patients with metastatic or unresectable melanoma, NSCLC, or carcinoma who received doses in the range: of 1 to 10 mg/kg bw every 2 weeks, 2 to 10 mg/kg bw every 3 weeks, or 200 mg every 3 weeks.

Absorption
Pembrolizumab is administered via the intravenous route and therefore is immediately and completely bioavailable.

Distribution
Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady-state is small (~6.0 L; CV: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Biotransformation
Pembrolizumab is catabolised through non-specific pathways; metabolism does not contribute to its clearance.

Elimination
Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady-state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Linearity/non-linearity
Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2.1-fold. The median trough concentrations (C_{min}) at steady-state were approximately 22 mcg/mL at a dose of 2 mg/kg bw every 3 weeks and 29 mcg/mL at a dose of 200 mg every 3 weeks. The median area under the concentration time curve at steady-state over 3 weeks ($AUC_{0\text{-}3weeks}$) was 794 mcg•day/mL at a dose of 2 mg/kg bw every 3 weeks and 1 053 mcg•day/mL at a dose of 200 mg every 3 weeks.

Following administration of pembrolizumab 200 mg every 3 weeks in patients with cHL, the observed median C_{min} at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in median C_{max} between cHL and other tumour types. Based on available safety data in cHL and other tumour types, these differences are not clinically meaningful.

Special populations
The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range: 15-94 years), gender, race, mild or moderate renal impairment, mild or moderate hepatic impairment and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. Pembrolizumab exposure with weight-based dosing at 2 mg/kg bw every 3 weeks in paediatric patients (≥ 3 to 17 years) are comparable to those of adults at the same dose.

Renal impairment
The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Pembrolizumab has not been studied in patients with severe renal impairment (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild and moderate hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered intravenous doses of 6, 40 or 200 mg/kg bw once a week in the 1-month study and once every two weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the no observed adverse effect level (NOAEL) in both studies was ≥ 200 mg/kg bw, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg bw, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

Animal reproduction studies have not been conducted with pembrolizumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss.

Animal fertility studies have not been conducted with pembrolizumab. In 1 month and 6 month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
2 years.

After preparation of infusion
Chemical and physical in-use stability has been demonstrated for up to 42 days at 2 °C to 8 °C or at 23 °C to 27 °C. Protect from light.
From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2 °C to 8 °C, or 12 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

4 mL of concentrate in a 10 mL Type I clear glass vial, with a coated grey chlorobutyl or bromobutyl stopper and an aluminium seal with a dark blue coloured flip-off cap, containing 100 mg pembrolizumab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation and administration of the infusion

- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25 °C).
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25 °C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 mL (total content per vial 4.25 mL) to ensure the recovery of 4 mL of concentrate. Mix diluted solution by gentle inversion.
- If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Translucent to white proteinaceous particles may be seen in diluted solution. Administer the infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2015
Date of latest renewal: 24 March 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

AstraZeneca Pharmaceuticals LP
Frederick Manufacturing Center (FMC)
633 Research Court
Frederick, Maryland 21703
U.S.

Boehringer Ingelheim (BIB)
Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
Germany

MSD Biotech B.V.
Vollenhovermeer 2
5347 JV Oss
The Netherlands

Boehringer Ingelheim Fremont, Inc. (BIF)
6701 Kaiser Drive
Fremont, California 94555
U.S.

MSD International GmbH (DUB)
Drynam Road
Swords, Dublin K67 P263
Ireland

Name and address of the manufacturers responsible for batch release

Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg
Belgium

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

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 PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of KEYTRUDA in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness of patients and/or their caregivers on the signs and symptoms relevant to the early recognition/identification of the potential immune-mediated adverse reactions (imARs).

The MAH shall ensure that in each Member State where KEYTRUDA is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe and use KEYTRUDA have access to/are provided with the patient educational material.

The patient educational material should contain:
- The patient card

The patient card shall contain the following key elements:
- Description of the main signs or symptoms of the imARs and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first
- The importance of carrying the patient card at all times and 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 KEYTRUDA.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
1. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P204: A Phase III, Randomised, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma – Final Study Report	4Q 2025
2. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing resected Stage II melanoma adjuvant study (KN716): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling	4Q 2024
3. Post-authorisation efficacy study (PAES) the MAH should submit the final study report of RFS/DMFS and OS data for study KN054: a Phase III Clinical Trial of Pembrolizumab (MK-3475) in Subjects with complete resection of high-risk Stage III melanoma – Final Study Report	4Q 2027
4. Post-authorisation efficacy study (PAES): in order to further characterise the efficacy of Keytruda in patients with MSI-H/dMMR gastric, biliary and small intestine cancers, the MAH should submit the results including ORR data from Cohort K and L of study KEYNOTE-158, a Phase II study investigating pembrolizumab (MK-3475) in previously treated patients with advanced solid tumours.	1Q 2025
5. Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of pembrolizumab as adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma, the MAH should submit the per-protocol specified interim analysis of OS for study KN716: A Phase III Clinical Trial of Pembrolizumab (MK–3475) in Subjects with complete resection of high-risk Stage II melanoma – Clinical Study Report	4Q 2028
6. Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of Keytruda for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence, the MAH should submit the results of the final OS analysis of study KEYNOTE-091. The MAH should submit updated data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab – Final Study Report	3Q 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab
100 mg/4 mL

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 4 mL contains 100 mg of pembrolizumab. Each mL of concentrate contains 25 mg of pembrolizumab.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution.
For single use only.
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

Do not shake.

8. EXPIRY DATE

EXP

The diluted solution may be stored for up to 7 days in a refrigerator (2 °C – 8 °C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C – 8 °C).
Do not Freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/002 (1 vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab
100 mg/4 mL
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KEYTRUDA is and what it is used for
2. What you need to know before you are given KEYTRUDA
3. How you are given KEYTRUDA
4. Possible side effects
5. How to store KEYTRUDA
6. Contents of the pack and other information

1. What KEYTRUDA is and what it is used for

KEYTRUDA contains the active substance pembrolizumab, which is a monoclonal antibody. KEYTRUDA works by helping your immune system fight your cancer.

KEYTRUDA is used in adults to treat:
- a kind of skin cancer called melanoma
- a kind of lung cancer called non-small cell lung cancer
- a kind of cancer called classical Hodgkin lymphoma
- a kind of cancer called bladder cancer (urothelial carcinoma)
- a kind of head and neck cancer called head and neck squamous cell carcinoma.
- a kind of kidney cancer called renal cell carcinoma
- a kind of cancer that is determined to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) in the colon or rectum (called colorectal cancer), uterus (called endometrial cancer), stomach (called gastric cancer), small bowel (called small intestine cancer), or bile duct or gallbladder (called biliary tract cancer)
- a kind of cancer called oesophageal carcinoma
- a kind of breast cancer called triple-negative breast cancer
- a kind of uterine cancer called endometrial carcinoma
- a kind of cancer called cervical cancer
- a kind of stomach cancer called gastric or gastro-oesophageal junction adenocarcinoma
- a kind of bile duct or gallbladder cancer called biliary tract carcinoma

KEYTRUDA is used in children and adolescents:
- aged 3 years and older to treat a kind of cancer called classical Hodgkin lymphoma
- aged 12 years and older to treat a kind of cancer called melanoma.

People get KEYTRUDA when their cancer has spread or cannot be taken out by surgery.

People get KEYTRUDA after they have had surgery to remove melanoma, non-small cell lung cancer or renal cell carcinoma to help prevent their cancer from coming back (adjuvant therapy).

People get KEYTRUDA before surgery (neoadjuvant therapy) to treat non-small cell lung cancer or triple-negative breast cancer and then continue getting KEYTRUDA after surgery (adjuvant therapy) to help prevent their cancer from coming back.

KEYTRUDA may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given KEYTRUDA

You should not be given KEYTRUDA
- if you are allergic to pembrolizumab 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 or nurse before receiving KEYTRUDA.

Before you get KEYTRUDA, tell your doctor if you:
- have an autoimmune disease (a condition where the body attacks its own cells)
- have pneumonia or inflammation of your lungs (called pneumonitis)
- were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine
- had an allergic reaction to other monoclonal antibody therapies
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have liver damage
- have kidney damage
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)

When you get KEYTRUDA, you can have some serious side effects. These side effects can sometimes become life-threatening and can lead to death. These side effects may happen anytime during treatment or even after your treatment has ended. You may experience more than one side effect at the same time.

If you have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment with KEYTRUDA.
- inflammation of the lungs, which may include shortness of breath, chest pain or coughing
- inflammation of the intestines, which may include diarrhoea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting
- inflammation of the liver, which may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal
- inflammation of the kidneys, which may include changes in the amount or colour of your urine
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- type 1 diabetes, including diabetic ketoacidosis (acid in the blood produced from diabetes), symptoms may include feeling more hungry or thirsty than usual, need to urinate more often or weight loss, feeling tired or 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
- inflammation of the eyes, which may include changes in eyesight
- inflammation in the muscles, which may include muscle pain or weakness
- inflammation of the heart muscle, which may include shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the pancreas, which may include abdominal pain, nausea and vomiting
- inflammation of the skin, which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis)
- 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)
- inflammation and scarring of the bile ducts, which may include pain in the upper right part of the stomach, swelling of the liver or spleen, fatigue, itching, or yellowing of the skin or the whites of eyes (cholangitis sclerosing)
- inflammation of the stomach (gastritis)
- decreased function of the parathyroid gland, which may include muscle cramps or spasms, fatigue and weakness (hypoparathyroidism)
- infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever

Complications, including graft-versus-host-disease (GVHD), in people with bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be severe and can lead to death. They may occur if you had this kind of transplant in the past or if you get it in the future. Your doctor will monitor you for signs and symptoms, which may include skin rash, liver inflammation, abdominal pain, or diarrhoea.

Children and adolescents
Do not give KEYTRUDA to children under 18 years of age, except for children:
- with classical Hodgkin lymphoma aged 3 years and older
- with melanoma aged 12 years and older.

Other medicines and KEYTRUDA
Tell your doctor
- If you are taking other medicines that make your immune system weak. Examples of these may include corticosteroids, such as prednisone. These medicines may interfere with the effect of KEYTRUDA. However, once you are treated with KEYTRUDA, your doctor may give you corticosteroids to reduce the side-effects that you may have with KEYTRUDA. Corticosteroids may also be given to you before receiving KEYTRUDA in combination with chemotherapy to prevent and/or treat nausea, vomiting, and other side effects caused by chemotherapy.
- If you are taking, have recently taken or might take any other medicines.

Pregnancy
- You must not use KEYTRUDA if you are pregnant unless your doctor specifically recommends it.
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.
- KEYTRUDA can cause harm or death to your unborn baby.
- If you are a woman who could become pregnant, you must use adequate birth control while you are being treated with KEYTRUDA and for at least 4 months after your last dose.

Breast-feeding
- If you are breast-feeding, tell your doctor.
- Do not breast-feed while taking KEYTRUDA.
- It is not known if KEYTRUDA passes into your breast milk.

Driving and using machines
KEYTRUDA has a minor effect on your ability to drive or use machines. Feeling dizzy, tired or weak are possible side effects of KEYTRUDA. Do not drive or use machines after you have been given KEYTRUDA unless you are sure you are feeling well.

3. How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of a doctor experienced in cancer treatment.
- The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks.
- The recommended dose of KEYTRUDA in children and adolescents aged 3 years and older with classical Hodgkin lymphoma and adolescents aged 12 years and older with melanoma, is 2 mg/kg bodyweight (up to a maximum of 200 mg) every 3 weeks.
- Your doctor will give you KEYTRUDA through an infusion into your vein (intravenous) for about 30 minutes.
- Your doctor will decide how many treatments you need.

If you miss an appointment to get KEYTRUDA
- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

If you stop receiving KEYTRUDA
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with KEYTRUDA unless you have discussed this with your doctor.

If you have any further questions about your treatment, ask your doctor.

You will also find this information in the patient card you have been given by your doctor. It is important that you keep this card and show it to your partner or caregivers.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get KEYTRUDA, you can have some serious side effects. See section 2.

The following side effects have been reported with pembrolizumab alone:

Very common (may affect more than 1 in 10 people)
- decrease in the number of red blood cells
- reduced thyroid gland activity
- feeling less hungry
- headache
- shortness of breath; cough
- diarrhoea; stomach pain; nausea; vomiting; constipation
- itching; skin rash
- pain in muscle and bones; joint pain
- feeling tired; unusual tiredness or weakness; swelling; fever

Common (may affect up to 1 in 10 people)
- lung infection
- decrease in the number of platelets (bruising or bleeding more easily); decrease in the number of white blood cell (neutrophils; lymphocytes)
- reactions related to the infusion of the medicine
- overactive thyroid gland; hot flush

- decreased sodium, potassium, or calcium in the blood
- trouble sleeping
- dizziness; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; lack of energy; change in your sense of taste
- dry eye
- abnormal heart rhythm
- high blood pressure
- inflammation of the lungs
- inflammation of the intestines; dry mouth
- inflammation of the liver
- red raised rash sometimes with blisters; inflammation of the skin; patches of skin which have lost colour; dry, itchy skin; hair loss; acne-like skin problem
- muscle pain, aches or tenderness; pain in arms or legs; joint pain with swelling
- flu-like illness; chills
- increased liver enzyme levels in the blood; increased calcium in the blood; abnormal kidney function test

Uncommon (may affect up to 1 in 100 people)
- a decreased number of white blood cells (leukocytes); inflammation response against platelets; an increased number of white blood cells (eosinophils)
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- decreased secretion of hormones produced by the adrenal glands; inflammation of the pituitary gland situated at the base of the brain; inflammation of the thyroid
- type 1 diabetes, including diabetic ketoacidosis
- a condition in which the muscles become weak and tire easily; seizure
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain; accumulation of fluid around the heart; inflammation of the covering of the heart
- inflammation of the pancreas; inflammation of the stomach; a sore that develops on the inside lining of your stomach or upper part of your small intestine
- thickened, sometimes scaly, skin growth; small skin bumps, lumps or sores; hair colour changes
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch

Rare (may affect up to 1 in 1 000 people)
- a condition called haemophagocytic lymphohistiocytosis, where the immune system makes too many infection fighting cells called histiocytes and lymphocytes that may cause various symptoms; inflammation response against red blood cells; feeling weak, lightheaded, short of breath or if your skin looks pale (signs of low level of red blood cells, possibly due to a type of anaemia called pure red cell aplasia)
- decreased function of the parathyroid gland, which may present as muscle cramps or spasms, fatigue and weakness
- a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome); inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis); 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); swelling of the optic nerve that may result in vision loss in one or both eyes, pain with eye movement, and/or loss of colour vision (optic neuritis); inflammation of the membrane around the spinal cord and brain, which may present as neck stiffness, headache, fever, eye sensitivity to light, nausea or vomiting (meningitis)
- inflammation of the blood vessels

- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency); a hole in the small intestines; coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- inflammation of the bile ducts
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (Stevens-Johnson syndrome or toxic epidermal necrolysis); tender red bumps under the skin
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)
- inflammation of the bladder, which may present as frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

Very common (may affect more than 1 in 10 people)
- decrease in the number of red blood cells; decreased number of white blood cells (neutrophils); decrease in the number of platelets (bruising or bleeding more easily)
- reduced thyroid gland activity
- decreased potassium in the blood; feeling less hungry
- trouble sleeping
- inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; headache
- shortness of breath; cough
- diarrhoea; vomiting; nausea; stomach pain; constipation
- hair loss; itching; skin rash
- pain in the muscles and bones; joint pain
- feeling tired; unusual tiredness or weakness; fever
- increased blood level of the liver enzyme alanine aminotransferase; increased blood level of the liver enzyme aspartate aminotransferase

Common (may affect up to 1 in 10 people)
- lung infection
- decreased number of white blood cells (neutrophils) with a fever; decreased number of white blood cells (leukocytes, lymphocytes)
- reaction related to the infusion of the medicine
- decreased secretion of hormones produced by the adrenal glands; inflammation of the thyroid; overactive thyroid gland
- decreased sodium or calcium in the blood
- dizziness; change in your sense of taste; lack of energy
- dry eye
- abnormal heart rhythm
- high blood pressure
- inflammation of the lungs
- inflammation of the intestines; inflammation of the stomach; dry mouth
- inflammation of the liver
- red raised rash, sometimes with blisters; inflammation of the skin; acne-like skin problem; dry, itchy skin
- muscle pain, aches or tenderness; pain in arms or legs; joint pain with swelling
- sudden kidney damage
- swelling; flu-like illness; chills
- increased bilirubin in the blood; increased blood level of the liver enzyme alkaline phosphatase; abnormal kidney function test; increased calcium in the blood

Uncommon (may affect up to 1 in 100 people)
- an increased number of white blood cells (eosinophils)
- inflammation of the pituitary gland situated at the base of the brain

- type 1 diabetes, including diabetic ketoacidosis
- inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis); seizure
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain; accumulation of fluid around the heart; inflammation of the covering of the heart
- inflammation of the blood vessels
- inflammation of the pancreas; a sore that develops on the inside lining of your stomach or upper part of your small intestine
- thickened, sometimes scaly, skin growth; patches of skin which have lost colour; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys; inflammation of the bladder, which may present as frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- increased level of amylase, an enzyme that breaks down starch

Rare (may affect up to 1 in 1 000 people)
- inflammation response against red blood cells or platelets
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- decreased function of the parathyroid gland, which may present as muscle cramps or spasms, fatigue and weakness
- a condition in which the muscles become weak and tire easily; a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome); swelling of the optic nerve that may result in vision loss in one or both eyes, pain with eye movement, and/or loss of colour vision (optic neuritis)
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency); a hole in the small intestines; coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- inflammation of the bile ducts
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (Stevens-Johnson syndrome); tender red bumps under the skin; hair colour changes
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

The following side effects have been reported in clinical studies with pembrolizumab in combination with axitinib or lenvatinib:

Very common (may affect more than 1 in 10 people)
- urinary infections (increased frequency in urination and pain in passing urine)
- decrease in the number of red blood cells
- reduced thyroid gland activity
- feeling less hungry
- headache; change in your sense of taste
- high blood pressure
- shortness of breath; cough
- diarrhoea; stomach pain; nausea; vomiting; constipation
- skin rash; itching
- joint pain; pain in the muscles and bones; muscle pain, aches or tenderness; pain in arms or legs
- feeling tired; unusual tiredness or weakness; swelling; fever
- increased levels of lipase, an enzyme that breaks down fats; increased liver enzyme levels in the blood; abnormal kidney function test

Common (may affect up to 1 in 10 people)
- lung infection

- decreased number of white blood cells (neutrophils, lymphocytes, leukocytes); decrease in the number of platelets (bruising or bleeding more easily)
- reaction related to the infusion of the medicine
- decreased secretion of hormones produced by the adrenal glands; overactive thyroid gland; inflammation of the thyroid
- decreased sodium, potassium, or calcium in the blood
- trouble sleeping
- dizziness; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; lack of energy
- dry eye
- abnormal heart rhythm
- inflammation of the lungs
- inflammation of the intestines; inflammation of the pancreas; inflammation of the stomach; dry mouth
- inflammation of the liver
- red raised rash, sometimes with blisters; inflammation of the skin; dry skin; acne-like skin problem; hair loss
- joint pain with swelling
- inflammation of the kidneys
- flu-like illness; chills
- increased levels of amylase, an enzyme that breaks down starch; increased bilirubin in the blood; increased blood levels of a liver enzyme known as alkaline phosphatase; increased calcium in the blood

Uncommon (may affect up to 1 in 100 people)
- an increased number of white blood cells (eosinophils)
- inflammation of the pituitary gland situated at the base of the brain
- type 1 diabetes, including diabetic ketoacidosis
- a condition in which the muscles become weak and tire easily; inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis)
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain; accumulation of fluid around the heart
- inflammation of the blood vessels
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- dry, itchy skin; thickened, sometimes scaly, skin growth; patches of skin which have lost colour; small skin bumps, lumps or sores; hair colour changes
- inflammation of the sheath that surrounds tendons

Rare (may affect up to 1 in 1 000 people)
- decreased function of the parathyroid gland, which may present as muscle cramps or spasms, fatigue and weakness
- swelling of the optic nerve that may result in vision loss in one or both eyes, pain with eye movement, and/or loss of colour vision (optic neuritis)
- a hole in the small intestines
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)
- inflammation of the bladder, which may present as frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency); coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

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 KEYTRUDA

Unopened vial
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 vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

After preparation of infusion
Chemical and physical in-use stability has been demonstrated for up to 42 days at 2 °C to 8 °C or at 23 °C to 27 °C. From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2 °C to 8 °C, or 12 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

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 KEYTRUDA contains
The active substance is pembrolizumab.

One vial of 4 mL contains 100 mg of pembrolizumab.
Each mL of concentrate contains 25 mg of pembrolizumab.

The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 and water for injections.

What KEYTRUDA looks like and contents of the pack
KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8.
It is available in cartons containing one glass vial.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Preparation and administration of the infusion

- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25 °C).
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25 °C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 mL (total content per vial 4.25 mL) to ensure the recovery of 4 mL of concentrate. Mix diluted solution by gentle inversion.
- Chemical and physical in-use stability has been demonstrated for up to 42 days at 2 °C to 8 °C or at 23 °C to 27 °C. Protect from light. From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2 °C to 8 °C, or 12 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Translucent to white proteinaceous particles may be seen in diluted solution. Administer the infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.