Informasi Untuk Pasien Tentang KEYTRUDA (pembrolizumab)
Injeksi

Silahkan membaca informasi ini dengan seksama sebelum anda menerima obat anda. Beberapa informasi mungkin telah berubah.

1. MENGAPA DOKTER SAYA MERESEPKAN KEYTRUDA?

KEYTRUDA digunakan untuk mengobati:

- salah satu jenis kanker kulit yang disebut melanoma pada dewasa
- salah satu jenis kanker yang disebut kanker paru jenis karsinoma bukan sel kecil (*NSCLC*) stadium lanjut maupun yang sudah menyebar pada dewasa yang tumornya mengekspresikan protein yang disebut dengan PD-L1 pada ≥ 50 % dari sel tumornya. Tumor pada pasien tidak boleh memiliki gen EGFR atau ALK yang abnormal dan belum pernah menerima kemoterapi sebelumnya untuk kanker parunya.
- salah satu jenis kanker yang disebut kanker paru jenis karsinoma bukan sel kecil (*NSCLC*) stadium lanjut pada dewasa yang tumornya mengekspresikan protein yang disebut dengan PD-L1 dan yang telah menerima kemoterapi mengandung platinum. Pasien dengan gen EGFR atau ALK abnormal harus sudah menerima terapi yang telah disetujui untuk kelainan tersebut sebelum menerima KEYTRUDA.
- salah satu jenis kanker yang disebut *mesothelioma* pleura ganas yang mempengaruhi lapisan paru-paru dan dinding dada pada orang dewasa
- salah satu jenis kanker kepala dan leher yang disebut sebagai karsinoma skuamous kepala dan leher pada dewasa yang tumornya mengekspresikan protein yang disebut dengan PD-L1
- salah satu jenis kanker yang disebut kanker esofagus pada dewasa
- salah satu jenis kanker lambung yang disebut *gastric cancer* atau *gastroesophageal junction adenocarcinoma* pada dewasa yang tumornya mengekspresikan protein yang disebut dengan PD-L1
- salah satu jenis kanker yang disebut karsinoma urotelial, termasuk kanker kandung kemih pada dewasa
- salah satu jenis kanker ginjal yang disebut karsinoma sel ginjal (KSG) pada

dewasa

- salah satu jenis kanker yang disebut limfoma hogdkin klasik (cHL) pada dewasa dan anak-anak
- salah satu jenis kanker yang disebut kanker kolon atau rektal pada dewasa, yang ditunjukkan oleh uji laboratorium sebagai *microsatelite instability-high* (MSI-H) atau *mismatch repair deficient* (dMMR).
- salah satu jenis kanker yang disebut kanker payudara *triple-negative* pada dewasa
- salah satu jenis kanker pada wanita dewasa yang disebut kanker serviks
- salah satu jenis kanker hati yang disebut karsinoma hepatoseluler pada dewasa
- salah satu jenis kanker rahim yang disebut karsinoma endometrium pada wanita dewasa
- salah satu jenis kanker saluran empedu atau kandung empedu yang disebut karsinoma saluran empedu pada dewasa

Pasien mendapatkan KEYTRUDA ketika kanker mereka telah menyebar atau tidak dapat diambil melalui tindakan operasi.

Pasien mendapatkan KEYTRUDA setelah mereka dioperasi untuk mengangkat melanoma, kanker paru jenis karsinoma bukan sel kecil, atau karsinoma sel ginjal untuk mencegah kanker kembali lagi.

Pasien mendapatkan KEYTRUDA sebelum mereka dioperasi untuk mengobati kanker paru bukan sel kecil, kanker kepala dan leher atau kanker payudara *triple-negative* dan penggunaan KEYTRUDA dilanjutkan kembali setelah operasi untuk mencegah kanker kembali lagi.

KEYTRUDA dapat diberikan secara kombinasi dengan obat anti kanker lain dengan atau tanpa terapi radiasi. Sangat penting bagi Anda juga membaca lembar informasi obat anti kanker lainnya yang digunakan. Jika Anda memiliki pertanyaan mengenai obat-obat ini, mohon tanyakan pada dokter Anda.

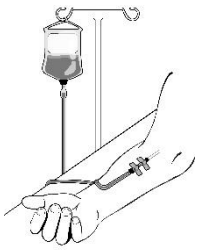
KEYTRUDA dapat diberikan secara kombinasi dengan agen kemoterapi pemetrexed dan platinum untuk pengobatan kanker paru yang disebut dengan kanker paru *non-squamous* NSCLC. KEYTRUDA dapat diberikan secara kombinasi dengan agen kemoterapi carboplatin dan paclitaxel untuk pengobatan kanker paru yang disebut dengan kanker paru *squamous* NSCLC. Penting bagi Anda untuk membaca brosur obat-obatan kemoterapi tersebut.

Apabila Anda memiliki pertanyaan mengenai obat-obatan ini, silahkan hubungi dokter Anda.

KEYTRUDA bekerja dengan membantu sistem kekebalan tubuh melawan kanker Anda.

2. BAGAIMANA ANDA AKAN MENERIMA KEYTRUDA?

- Dokter akan memberikan KEYTRUDA melalui suntikan intravena selama sekitar 30 menit.
- Kebanyakan pasien mendapatkan KEYTRUDA setiap 3 minggu atau 6 minggu, tergantung pada dosis yang diberikan.
- Dokter anda akan memutuskan berapa banyak obat yang anda butuhkan.



Dosis KEYTRUDA yang direkomendasikan adalah:

- 200 mg untuk: pengobatan tambahan NSCLC, pengobatan tambahan melanoma, NSCLC yang belum diobati sebelumnya, karsinoma skuamous kepala dan leher (HNSCC), kanker esofagus, karsinoma urotelial, karsinoma sel ginjal (KSG), cHL, kanker kolorektal, kanker payudara *triple-negative,* kanker serviks, karsinoma hepatoseluler, karsinoma saluran empedu, pengobatan lini pertama kanker lambung sebagai terapi kombinasi, atau *mesothelioma* pleura ganas (MPM)
- 200 mg setiap 3 minggu atau 400 mg setiap 6 minggu untuk HNSCC

stadium lanjut lokal yang dapat dihilangkan dengan pembedahan (*resectable*)

- 200 mg atau 400 mg untuk karsinoma endometrium dengan terapi kombinasi
- 2 mg/kg untuk: kanker kulit yang tidak dapat dihilangkan dengan pembedahan (*unresectable*) atau yang telah menyebar, atau *NSCLC* yang telah diobati sebelumnya sebagai agen tunggal

Untuk kanker paru jenis non squamous NSCLC, KEYTRUDA diberikan dalam kombinasi dengan obat kemoterapi yaitu pemetrexed dan platinum selama 4 siklus dilanjutkan dengan kombinasi KEYTRUDA dan Pemetrexed hingga terjadi progresi penyakit.

Untuk kanker paru jenis Squamous NSCLC, pasien mendapatkan KEYTRUDA kombinasi dengan Kemoterapi Karboplatin dan Paclitaxel selama 4 siklus dan dilanjutkan dengan Pembrolizumab secara tunggal hingga terjadi progresi penyakit.

2.1 Bagaimana jika anda melewatkan jadwal anda untuk mendapatkan KEYTRUDA?

- Hubungi dokter segera untuk menjadwal ulang pertemuan anda.
- Penting untuk diperhatikan bahwa anda tidak boleh melewatkan dosis obat ini.

3. APA YANG HARUS SAYA TAHU SEBELUM DAN SAAT MENERIMA KEYTRUDA?

3.1 Siapa yang sebaiknya tidak diberikan KEYTRUDA?

Anda tidak dapat diberikan KEYTRUDA jika anda alergi terhadap pembrolizumab atau salah satu bahan lain yang terkandung dalam KEYTRUDA.

3.2 Apa yang harus saya katakan pada dokter sebelum dan saat menerima KEYTRUDA?

Sebelum anda mendapatkan KEYTRUDA, beritahu dokter anda jika anda:

- memiliki penyakit sistem kekebalan tubuh seperti *Crohn's*, kolitis ulserativa

atau lupus

- memiliki transplantasi organ (seperti transplantasi ginjal) atau memiliki transplantasi tulang belakang (sel punca) yang menggunakan donor sel punca (alogenik)
- memiliki pneumonia atau pembengkakan paru-paru (disebut pneumonitis)
- memiliki kerusakan hati

3.3 Kehamilan

- Jika anda sedang hamil, merasa hamil atau berencana untuk punya bayi, beritahu dokter anda.
- KEYTRUDA dapat menyebabkan kerusakan atau kematian janin.
- Anda harus menggunakan kontrasepsi efektif saat anda sedang dirawat dengan KEYTRUDA dan setidaknya 4 bulan setelah dosis terakhir KEYTRUDA jika anda seorang wanita yang bisa hamil.

3.4 Menyusui

- Jika anda sedang menyusui, beritahu dokter Anda.
- Jangan menyusui saat menggunakan KEYTRUDA.

3.5 Anak-anak

KEYTRUDA dapat digunakan pada anak-anak dengan limfoma Hodgkin klasik.

3.6 Dapatkah saya menerima KEYTRUDA dengan obat lain, suplemen makanan, produk herbal atau makanan?

Katakan kepada dokter anda

- Tentang semua obat-obatan yang anda gunakan, termasuk obat-obatan resep dan non-resep, vitamin dan suplemen herbal.
- Jika anda menggunakan obat-obatan lain yang membuat sistem kekebalan tubuh anda lemah. Contoh obat-obatan ini bisa termasuk steroid, seperti prednison.

3.7 Apakah saya boleh mengemudi dan mengoperasikan mesin saat menggunakan KEYTRUDA?

Jangan mengendarai atau menggunakan mesin setelah anda diberikan KEYTRUDA kecuali anda yakin anda merasa baik. Merasa lelah atau lemah

adalah efek samping dari KEYTRUDA. Hal ini dapat mempengaruhi kemampuan mengemudi atau menggunakan mesin.

4. APA EFEK YANG TIDAK DIINGINKAN YANG DISEBABKAN OLEH KEYTRUDA?

Ketika anda mendapatkan KEYTRUDA, anda dapat memiliki beberapa efek samping yang serius.

Efek samping ini terkadang dapat mengancam nyawa yang berujung pada kematian. Efek samping ini dapat terjadi kapan saja selama pengobatan atau setelah pengobatan selesai. Anda mungkin mengalami lebih dari satu efek samping pada waktu yang bersamaan.

Jika anda memiliki salah satu dari gejala berikut, telephone atau pergi ke dokter anda segera.

- **Tanda dan gejala masalah paru-paru**
  - sesak napas
  - nyeri dada
  - batuk

- **Tanda dan gejala masalah dengan usus anda**
  - diare atau buang air besar lebih dari biasanya
  - tinja anda berwarna hitam, seperti ter, lengket, atau memiliki darah atau lendir
  - sakit perut yang parah atau nyeri

- **Tanda dan gejala masalah hati**
  - mual atau muntah
  - merasa tidak lapar
  - nyeri di sisi kanan perut anda
  - kulit anda terlihat kuning
  - bagian putih mata anda tampak kuning
  - urin gelap
  - anda berdarah atau memar lebih mudah dari biasanya

- **Tanda dan gejala masalah ginjal**
  - perubahan dalam jumlah atau warna urin anda

- **Tanda dan gejala masalah kelenjar hormon (terutama tiroid, hipofisis, dan kelenjar adrenal)**
  - jantung berdetak cepat
  - penurunan berat badan
  - lebih berkeringat
  - berat badan bertambah
  - rambut rontok
  - merasa dingin
  - sembelit
  - suara anda akan lebih berat
  - nyeri otot
  - pusing atau pingsan
  - sakit kepala yang tidak bisa hilang atau sakit kepala yang tidak biasa

- **Tanda dan gejala masalah gula darah**
  - merasa lebih lapar atau haus
  - keinginan buang air kecil lebih sering
  - penurunan berat badan

- **Tanda dan gejala masalah kulit**
  - ruam
  - gatal
  - kulit melepuh, mengelupas, atau perih
  - luka (borok) pada mulut, lapisan hidung, tenggorokan atau area kelamin

- **Tanda dan gejala masalah di organ lain:**
  - Nyeri otot atau lemah otot
  - Perubahan penglihatan
  - Peradangan pankreas
  - Kebingungan, demam, masalah pada ingatan, atau kejang (*encephalitis*)
  - Pembengkakan kelenjar getah bening, ruam atau benjolan lunak pada kulit, batuk, atau rasa sakit di mata (*sarcoidosis*)

- Nafas yang pendek, detak jantung yang tidak teratur, merasa lelah, atau sakit pada bagian dada (miokarditis, perikarditis)
- Nyeri, kebas, sensasi menggelitik, atau rasa lemah pada lengan atau kaki; masalah kandung kemih atau usus termasuk keinginan buang air kecil lebih sering, inkontinensia urin, kesulitan buang air kecil dan sembelit (*myelitis*)
- Peradangan pada pembuluh darah (*vasculitis*)
- Penurunan fungsi kelenjar paratiroid, yang dapat termasuk kram atau kejang otot, kelelahan dan rasa lemah (hipoparatiroidisme)
- Peradangan pada lapisan lambung, yang mungkin termasuk sakit perut yang parah atau nyeri, mual atau muntah (gastritis)
- Kerusakan pada sel darah merah, yang mungkin termasuk urin berwarna gelap, kulit/mata pucat atau kuning, sakit kepala ringan, rasa lelah, jantung berdetak cepat, atau sesak napas (anemia hemolitik)
- Nyeri pada bagian atas kanan dari perut, pembengkakan pada hati atau limpa, kelelahan, rasa gatal, atau kulit yang menguning atau bagian putih pada mata yang menguning (*sclerosing cholangitis*)
- Penurunan kemampuan pankreas untuk memproduksi enzim pencernaan, yang mungkin termasuk diare dengan tinja encer dan berminyak, penurunan berat badan, penyakit tulang metabolik, dan kekurangan vitamin atau mineral (insufisiensi pankreas eksokrin)

Terdapat beberapa kemungkinan efek samping penggunaan KEYTRUDA pada pasien yang menerima transplantasi:

• **Penolakan organ transplan**. Pasien yang pernah menerima organ transplan, mengalami peningkatan resiko penolakan organ transplan. Dokter Anda seharusnya memberitahukan tanda-tanda dan gejala yang seharusnya Anda laporkan dan mengawasi Anda, bergantung pada tipe organ transplan yang Anda terima.

• **Penyakit *Graft-versus-host-disease (GVHD)* pada pasien dengan transplan tulang belakang (sel punca) yang menggunakan donor sel punca (alogenik).** GVHD dapat terjadi jika Anda pernah menerima transplantasi ini sebelumnya. Dokter

Anda akan mengawasi Anda ketika terdapat tanda dan gejala berikut: ruam kulit, inflamasi pada hati, rasa sakit dibagian perut, dan diare.

- **Tanda dan gejala reaksi infus (IV):**
  - Sesak napas
  - gatal atau ruam
  - pusing
  - demam

- **Efek samping yang paling umum ketika KEYTRUDA diberikan sendiri termasuk:**
  - gatal
  - nafsu makan menurun
  - sesak napas
  - mual
  - kadar hormon tiroid yang rendah

- **Efek samping yang paling umum ketika KEYTRUDA diberikan secara tunggal kepada anak-anak termasuk:**
  - demam
  - muntah
  - sakit kepala
  - sakit perut
  - penurunan jumlah sel darah merah
  - batuk
  - konstipasi

- **Efek samping paling umum ketika KEYTRUDA diberikan dalam kombinasi bersama kemoterapi atau kemoterapi dengan terapi radiasi adalah:**
  - rambut rontok
  - kelelahan
  - diare
  - muntah
  - ruam

- demam
- penurunan sel darah putih
- penurunan nafsu makan
- nyeri sendi
- pembengkakan lapisan sistem pencernaan (contohnya mulut, usus)
- luka pada mulut
- penurunan pada jumlah sel darah merah
- penurunan pada jumlah platelet dalam darah
- kadar hormon tiroid yang rendah
- penurunan berat badan

- **Efek samping yang paling umum ketika KEYTRUDA diberikan secara kombinasi dengan aksitinib adalah:**
  - diare
  - tekanan darah tinggi
  - kelelahan
  - kadar hormon tiroid yang rendah
  - penurunan nafsu makan
  - lepuhan atau kemerahan pada telapak tangan atau telapak kaki Anda
  - mual
  - peningkatan kadar enzim hati
  - suara serak
  - batuk
  - konstipasi

- **Efek samping yang paling umum ketika KEYTRUDA diberikan secara kombinasi dengan lenvatinib adalah:**
  - tekanan darah tinggi
  - diare
  - merasa lelah
  - penurunan nafsu makan
  - kadar hormon tiroid yang rendah
  - mual
  - muntah

- luka pada mulut
- penurunan berat badan
- nyeri sendi
- sakit kepala
- konstipasi
- suara serak
- infeksi saluran kemih
- rasa sakit pada daerah perut (*abdominal*)
- kadar magnesium yang rendah
- lepuhan atau kemerahan pada telapak tangan atau telapak kaki Anda
- sesak napas
- batuk
- nyeri otot
- sakit punggung
- ruam
- protein dalam urin Anda
- peningkatan kadar enzim hati
- merasa lemah

Efek samping yang kurang umum bisa terjadi.

Selain itu, dokter mungkin melakukan tes darah untuk memeriksa efek samping.

KEYTRUDA dapat menyebabkan efek samping lainnya yang tidak terdaftar. Untuk informasi lebih lanjut, tanyakan kepada dokter anda.

Jika anda memiliki efek samping yang mengganggu anda atau yang tidak hilang, beritahu dokter anda.

5. APAKAH KEYTRUDA?

KEYTRUDA (pembrolizumab) tersedia sebagai:

- botol berisi 100 mg bahan aktif, pembrolizumab, dalam 4 mL larutan.

KEYTRUDA berupa larutan jernih atau sedikit opalescent, tidak berwarna atau agak kekuningan.

6. BAGAIMANA SEHARUSNYA SAYA MENYIMPAN KEYTRUDA?

Simpan di suhu 2-8°C.

Stabilitas penggunaan kimia dan fisik telah dibuktikan hingga 42 hari pada suhu 2°C hingga 8°C atau 23°C hingga 27°C. Produk ini tidak mengandung bahan pengawet. Penanganan aseptik harus dipastikan selama persiapan infus. Produk yang sudah diencerkan harus digunakan segera. Jika tidak segera digunakan, larutan infus KEYTRUDA dapat disimpan pada suhu kamar hingga 12 jam. Larutan infus KEYTRUDA juga dapat disimpan dalam lemari pendingin pada 2°C sampai 8°C; Namun, total waktu dari pengenceran KEYTRUDA sampai proses infus selesai tidak boleh melebihi 7 hari. Jika disimpan dalam lemari pendingin, biarkan vial atau infus di suhu kamar sebelum digunakan.

Jauhkan KEYTRUDA dan semua obat dari jangkauan anak-anak.

7. BAGAIMANA SAYA DAPAT BELAJAR LEBIH TENTANG KEYTRUDA DAN KONDISI SAYA?

Anda dapat memperoleh informasi lebih lanjut dari dokter anda.

Box, 1 vial @ 4 mL, Reg No. DKI2363501649A1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Didaftarkan oleh:
PT Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

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Jakarta, Indonesia

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Dikemas & dirilis oleh:
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Anda dapat melaporkan efek samping secara langsung melalui:

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KEYTRUDA (pembrolizumab)
injection

1. INDICATIONS AND USAGE

Melanoma
KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the treatment of adult patients with Stage IIB or IIC melanoma who have undergone complete resection.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.

Non-Small Cell Lung Carcinoma
Combination Therapy
Non squamous NSCLC
KEYTRUDA, in combination with pemetrexed and platinum chemotherapy (triple combination), is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

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

Monotherapy
KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 with a ≥50% tumor proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

KEYTRUDA is indicated for the treatment of patients with advanced NSCLC whose tumors express PD-L1 as determined by a validated test and who have received

platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have received approved therapy for these aberrations prior to receiving KEYTRUDA *[See Clinical Studies (9)]*.

KEYTRUDA as monotherapy is indicated for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II NSCLC.

Neoadjuvant and Adjuvant Therapy
KEYTRUDA is indicated for the treatment of patients with resectable Stage II, IIIA or IIIB (T3-4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

Malignant Pleural Mesothelioma
KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for adults with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and Neck Cancer
KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced, non nasopharyngeal head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 [Combined Positive Score (CPS ≥1)], as monotherapy as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as monotherapy.

KEYTRUDA, as monotherapy is indicated for the treatment of patients with metastatic or unresectable recurrent non nasopharyngeal HNSCC, whose tumors express PD-L1 [Combined Positive Score (CPS ≥1)].

KEYTRUDA, in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the treatment of patients with metastatic or unresectable recurrent non

nasopharyngeal HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS ≥1)].

Oesophageal Carcinoma

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥10.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with recurrent locally advanced or metastatic esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, and who have received one prior line of systemic therapy.

Gastric Cancer

KEYTRUDA in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with CPS ≥1.

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Urothelial Carcinoma

KEYTRUDA (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of

patients with intermediate/poor risk advanced renal cell carcinoma (RCC).

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

KEYTRUDA, as monotherapy, 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 (for selection criteria, please see Section 9. Clinical Studies).

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL) that has relapsed after two or more lines of therapy.

Colorectal Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

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 monotherapy as adjuvant treatment after surgery.

KEYTRUDA, in combination with paclitaxel, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by a validated test.

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 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Biliary Tract Carcinoma

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

Endometrial Carcinoma

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

KEYTRUDA, in combination with chemotherapy (carboplatin and paclitaxel), followed by KEYTRUDA as monotherapy, is indicated for the treatment of patients with primary advanced or recurrent endometrial carcinoma.

2. DOSAGE AND ADMINISTRATION

2.1 General

Patient Selection

If specified in the indication, select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression [see *Indications and Usage (1)*].

PD-L1 expression should be evaluated using validated test kit.

Select patients with unresectable or metastatic CRC for treatment with KEYTRUDA based on MSI-H or dMMR tumor status [see *Clinical Studies (9)*].

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA is:

- 200 mg every 3 weeks for: the adjuvant treatment of NSCLC, the adjuvant treatment of melanoma, previously untreated NSCLC, HNSCC, esophageal cancer, urothelial carcinoma, RCC, cHL, colorectal cancer, triple-negative breast cancer, cervical cancer, hepatocellular carcinoma, biliary tract carcinoma, first-line treatment of gastric cancer as combination therapy, or MPM
- 200 mg every 3 weeks or 400 mg every 6 weeks for resectable locally advanced HNSCC
- 200 mg every 3 weeks or 400 mg every 6 weeks for endometrial carcinoma in combination therapy
- 2 mg/kg every 3 weeks for unresectable or metastatic melanoma or previously treated NSCLC as monotherapy

For FIGO 2014 Stage III-IVA cervical cancer, the recommended dose of KEYTRUDA in combination with CRT is 200 mg every 3 weeks followed by KEYTRUDA 400 mg every 6 weeks as monotherapy administered as an intravenous infusion over 30 minutes.

For use in combination, see the prescribing information for the concomitant therapies.

For RCC patients treated with KEYTRUDA in combination with axitinib, see the prescribing information regarding dosing of axitinib. When 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 *[see Clinical Studies (9)]*

For RCC patients treated with KEYTRUDA in combination with lenvatinib, the recommended initial dose of lenvatinib is 20 mg orally once daily until disease progression or unacceptable toxicity.

For endometrial carcinoma patients treated with KEYTRUDA in combination with lenvatinib, the recommended initial dose of lenvatinib is 20 mg orally once daily until disease progression or unacceptable toxicity.

For primary advanced or recurrent endometrial carcinoma, the recommended dose of KEYTRUDA in combination with chemotherapy is 200 mg every 3 weeks followed by KEYTRUDA 400 mg every 6 weeks as monotherapy.

For the adjuvant treatment of melanoma, KEYTRUDA is administered until disease recurrence or unacceptable toxicity. The current available data for KEYTRUDA is limited up to one year. Post lymph node dissection radiotherapy, if indicated, should have been completed within the 13 week post-surgery period and prior to treatment start.

For the adjuvant treatment of NSCLC or RCC, KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA 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 monotherapy for 39 weeks or until disease recurrence or unacceptable toxicity.

The use of pembrolizumab in combination with pemetrexed and platinum chemotherapy showed the greater PD-L1 expression status the better the efficacy. See detail information in the Clinical Studies section.

The use of pembrolizumab in combination with carboplatin and paclitaxel showed the highest Overall Survival in population with PD-L1 expression 1-49%. See detail information in the Clinical Studies section.

When administering KEYTRUDA as part of a combination with chemotherapy, KEYTRUDA should be administered first. See also the prescribing information for the chemotherapy agents administered in combination.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumor size or small new lesions within the first few months followed by tumor shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression should remain on treatment until disease progression is confirmed.

When KEYTRUDA is given as a triple combination for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations, the triple combination is given for 4 cycles and continued with combination of KEYTRUDA with pemetrexed until disease progression.

Patients with squamous cell NSCLC should be treated with triple combination (pembrolizumab, carboplatin, and paclitaxel) for 4 cycles and continued with pembrolizumab alone until disease progression.

For the neoadjuvant and adjuvant treatment of high-risk early-stage 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.

Neoadjuvant treatment with KEYTRUDA for 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, continued as adjuvant treatment in combination with RT with or without chemotherapy for 3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks followed by 12 doses of 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks as monotherapy or until disease recurrence or unacceptable toxicity.

Dose modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described below.

Table 1: Recommended Dose Modifications *[see Warnings and Precautions (4)]*

Adverse reactions	Severity	Dose modification

Immune-mediated pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) or recurrent moderate (Grade 2)	Permanently discontinue
Immune-mediated colitis	Moderate or severe (Grade 2 or 3)	Withhold until adverse reactions recover to Grade 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Immune-mediated nephritis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4)	Permanently discontinue
Immune-mediated endocrinopathies	Severe or life-threatening (Grade 3 or 4)	Withhold until adverse reactions recover to Grade 0-1* For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.
Immune-mediated hepatitis/non-HCC	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times upper limit of normal	Withhold until adverse reactions recover to Grade 0-1*

For liver enzyme elevations in RCC patients treated with combination therapy with axitinib, see dosing guidelines following this table	(ULN) or total bilirubin >1.5 to 3 times ULN	
	AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue
	For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week	Permanently discontinue
Immune-mediated hepatitis/HCC	AST or ALT with baseline <2 times ULN and increases to ≥5 times ULN; AST or ALT with baseline ≥2 times ULN and increases to >3 times baseline; or AST or ALT >500 U/L regardless of baseline levels Total bilirubin with baseline levels <1.5 mg/dL and increases to >2 mg/dL; total bilirubin with baseline levels ≥1.5 mg/dL and increases to ≥2 times baseline; or total bilirubin >3.0 mg/dL regardless of baseline levels	Withhold until adverse reactions recover to Grades 0-1*
	ALT >20 times ULN; Child Pugh score ≥9 points; gastrointestinal bleeding suggestive of portal hypertension; ascites; or encephalopathy	Permanently discontinue

Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grade 0-1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (Grade 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 corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

In patients with cHL with Grade 4 hematological toxicity, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1.

Combination Therapy

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, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. 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.

- If ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

When administering KEYTRUDA in combination with lenvatinib, interrupt one or both or dose reduce or discontinue lenvatinib to manage adverse reactions as appropriate. For recommendations for management of adverse reactions of lenvatinib, refer to the prescribing information for lenvatinib. No dose reductions are recommended for KEYTRUDA.

Preparation and administration

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Do not freeze the infusion solution.
- Chemical and physical in-use stability has been demonstrated for up to 42 days at 2°C to 8°C or 23°C to 27°C.
- The product does not contain preservative. Aseptic handling should be ensured during the preparation of infusion. The diluted product should be used immediately. If not used immediately, diluted solutions of KEYTRUDA may be stored at room temperature for up to 12 hours. Diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from dilution of KEYTRUDA to completion of infusion should not exceed 7 days. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

- Translucent to white proteinaceous particles may be seen in the diluted solution. Administer 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 drugs through the same infusion line.
- Discard any unused portion left in the vial.

2.2 Pediatric Patients

In cHL, the recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks.

2.3 Geriatric Patients

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population.

2.4 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.

2.5 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.

3. CONTRAINDICATIONS

KEYTRUDA is contraindicated in patients with hypersensitivity to pembrolizumab or any of the inactive ingredients.

4. WARNINGS AND PRECAUTIONS

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 KEYTRUDA. Immune-mediated adverse reactions can occur after discontinuation of treatment. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.1) and Adverse Reactions (7.1).]*

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7.1)]*. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7.1)]*. Monitor patients for signs and symptoms of colitis and exclude other causes. Administer

corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7.1)]*. Monitor patients 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 exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7.1)]*. Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA. *[See Adverse Reactions (7.1).]* Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7.1)]*. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment; therefore, monitor patients 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. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism. *[See Dosage and Administration (2.1), Adverse Reactions (7.1), and Immune-mediated adverse reactions above.]*

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids *[see Dosage and Administration (2.1)]*.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.1)]*.

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 : uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, vasculitis, hypoparathyroidism, gastritis, haemolytic anaemia, and pericarditis. The following were reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis, sclerosing cholangitis, and exocrine pancreatic insufficiency.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in post-marketing use.

Transplant-related adverse reactions

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

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with KEYTRUDA has been reported in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone (off labeled combination)

In two randomized clinical 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 clinical trials.

Elevated liver enzymes when KEYTRUDA is given in combination with axitinib for RCC

When KEYTRUDA 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 Adverse Reactions (7.1)]*. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. *[See Dosage and Administration (2.1) and the prescribing information for axitinib.]*

Infusion-related reactions

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.1)]*. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA. 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 KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions. *[See Warnings and Precautions (4).]*

Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, 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. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months after the last dose of KEYTRUDA.

6.2 Nursing Mothers

It is unknown whether KEYTRUDA is secreted in human milk. Because many drugs are secreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA, taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA therapy for the woman.

6.3 Pediatric Use

In KEYNOTE-051, 161 pediatric patients (62 children ages 6 months to less than 12 years and 99 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 4 doses (range 1-35 doses), with 138 patients (86%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of

pediatric patients) were pyrexia, vomiting, headache, abdominal pain, anemia, cough, and constipation.

Efficacy for pediatric patients with cHL is extrapolated from the results in the respective adult populations [*see Clinical Studies (9)*].

6.4 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 Animal Toxicology (11.5)].*

6.5 Effects on ability to drive and use machines

Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab.

7. ADVERSE REACTIONS

7.1 Clinical Trials Experience

The safety of KEYTRUDA was evaluated in 2799 patients in controlled and uncontrolled studies. The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year. KEYTRUDA was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA. Of these treatment-related SAEs, the most common were pneumonitis, colitis, diarrhea, and pyrexia.

Immune-mediated adverse reactions *[see Warnings and Precautions (4)]:*

Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. Table 2 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA.

Table 2: Immune-mediated Adverse Reactions

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2799				
Adverse Reaction	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Hypothyroidism*	8.5	6.2	0.1	0	0
Hyperthyroidism†	3.4	0.8	0.1	0	0
Pneumonitis‡	3.4	1.3	0.9	0.3	0.1
Colitis	1.7	0.4	1.1	<0.1	0
Adrenal Insufficiency	0.8	0.3	0.3	<0.1	0
Hepatitis	0.7	0.1	0.4	<0.1	0
Hypophysitis	0.6	0.2	0.3	<0.1	0
Nephritis§	0.3	0.1	0.1	<0.1	0
Type 1 Diabetes Mellitus	0.2	<0.1	0.1	0.1	0

* In individual studies of patients with HNSCC treated with KEYTRUDA as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA 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 with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2.

In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hypothyroidism was 21% (all Grades) with 0.2% Grade 3.

† In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=984) the incidence of hyperthyroidism was 12% (all Grades) with 0.2% Grade 3.

‡ In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, 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.

§ In patients with non-squamous NSCLC treated with KEYTRUDA 200 mg in combination with pemetrexed and platinum chemotherapy (n=405) the incidence of nephritis was 1.7% (all Grades) with 1.0% Grade 3 and 0.5% Grade 4.

Endocrinopathies: The median time to onset of adrenal insufficiency was 5.3 months (range 26 days to 16.6 months). The median duration was not reached (range 4 days to 1.9+ years). Adrenal insufficiency led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Adrenal insufficiency resolved in 5 patients. The median time to onset of

hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.

Pneumonitis: The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.

Colitis: The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.

Hepatitis: The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.

Nephritis: The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients.

Other adverse events

Melanoma

Table 3 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse event (reported in at least 15% of patients) were arthralgia and cough.

Table 3: Adverse Events Occurring in ≥10% of Patients treated with KEYTRUDA and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab 3 mg/kg every 3 weeks n=256	
Adverse Events	All Grades (%)	Grade 3* (%)	All Grades (%)	Grade 3* (%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0	10	1
Back pain	12	1	7	1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0
Skin And Subcutaneous Tissue Disorders				
Vitiligo	11	0	2	0

* Of these ≥10% adverse events, none was reported as Grade 4.

Table 4 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA at a dose of 2 mg/kg dose in KEYNOTE-002. The most common adverse events (reported in at least 20% of patients) was pruritus.

Table 4: Adverse Events Occurring in ≥10% of Patients with Melanoma Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

	KEYTRUDA 2 mg/kg every 3 weeks n=178		Chemotherapy n=171	
Adverse Event	All Grades (%)	Grade 3-4* (%)	All Grades (%)	Grade 3-4* (%)
Gastrointestinal Disorders				
Abdominal pain	13	2	8	1

Skin And Subcutaneous Tissue Disorders				
Pruritus	25	0	8	0
Rash	13	0	8	0
Metabolism and Nutrition Disorders				
Hyponatremia	11	3	5	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	1	10	1

* Of these ≥ 10% adverse events, none was reported as Grade 4 in patients receiving KEYTRUDA at 2 mg/kg. Hyponatremia was reported as Grade 4 in one patient receiving chemotherapy.

Overall, the safety profile was similar across all doses and between patients previously treated with ipilimumab and patients naïve to treatment with ipilimumab.

Resected Melanoma

Among the 969 patients with resected melanoma enrolled in KEYNOTE-716 and 1019 patients with resected melanoma enrolled in KEYNOTE-054, the adverse reactions were generally similar to those occurring in patients with unresectable or metastatic melanoma or NSCLC.

Non Small Cell Lung Carcinoma

Combination Therapy

Table 5 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA, pemetrexed, and platinum chemotherapy in KEYNOTE-189.

Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel in KEYNOTE-407 were generally similar to those occurring in patients in KEYNOTE-189 with the exception of alopecia (46%) and arthralgia (21%).

Table 5: Adverse events occurring in ≥20% of patients receiving KEYTRUDA with pemetrexed and platinum chemotherapy and at a higher incidence than in patients receiving placebo with pemetrexed and platinum chemotherapy (between-arm difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-189)

	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=405		Placebo + Pemetrexed + Platinum Chemotherapy n=202	
Adverse Events	All Grades* (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue	41	6	38	2.5
Asthenia	20	6	24	3.5
Gastrointestinal Disorders				
Diarrhea	31	5	21	3.0
Blood and Lymphatic System Disorders				
Neutropenia	27	16	24	12
Skin and Subcutaneous Tissue Disorders				
Rash	20	1.7	11	1.5

* Graded per NCI CTCAE v4.03

Monotherapy

Table 6 summarizes the adverse events that occurred in at least 10% of patients with NSCLC treated with KEYTRUDA in KEYNOTE-010. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-024 were generally similar to those occurring in patients in KEYNOTE-010.

Table 6: Selected* Adverse Events Occurring in ≥10% of NSCLC Patients Treated with KEYTRUDA (KEYNOTE-010)

	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m² every 3 weeks n=309	
Adverse Event	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased appetite	25	1.5	23	2.6
Gastrointestinal Disorders				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	11	1.0	9	0.3
Back pain	11	1.5	8	0.3
Skin and Subcutaneous Tissue Disorders				
Rash	17	0.4	8	0
Pruritus	11	0	3	0.3

* Adverse events 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

Table 7: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA (KEYNOTE-010)

	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m² every 3 weeks	
Laboratory Test †	**All Grades‡ %**	**Grades 3-4 %**	**All Grades‡ %**	**Grades 3-4 %**
Chemistry				
Hyponatremia	32	8	27	2.9
Alkaline phosphatase increased	28	3.0	16	0.7
Aspartate aminotransferase increased	26	1.6	12	0.7
Alanine aminotransferase increased	22	2.7	9	0.7

* 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

Neoadjuvant and Adjuvant Therapy for Resectable NSCLC

Adverse events occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

Adjuvant Therapy for Resected NSCLC

Among the 580 patients with resected NSCLC treated with KEYTRUDA in KEYNOTE-091, the adverse reactions were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as monotherapy with the exception of hypothyroidism (21%) and hyperthyroidism (11%).

Other Cancers

Monotherapy

Adverse events occurring in patients with HNSCC, esophageal cancer, urothelial carcinoma, cHL, CRC, adjuvant treatment of RCC, or HCC were generally similar to those occurring in patients with melanoma or NSCLC.

Combination Therapy

Malignant Pleural Mesothelioma

Among the 241 patients with MPM treated with KEYTRUDA in combination with pemetrexed and platinum chemotherapy in KEYNOTE-483, the adverse events were generally similar to those occurring in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

Head and Neck Cancer

In patients with HNSCC receiving KEYTRUDA as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin and then as monotherapy, the adverse event occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity for KEYTRUDA plus RT with or without cisplatin compared to RT with or without cisplatin was weight loss (14% vs. 10%).

In patients with HNSCC receiving KEYTRUDA plus chemotherapy (platinum and 5-FU), adverse events occurring at a greater severity (Grades 3-4) and at a higher incidence (≥2% difference) compared to cetuximab plus chemotherapy (platinum and 5-FU) were: fatigue (7% vs. 4.9%), mucosal inflammation (10% vs. 5%), and stomatitis (8% vs. 3.5%).

Esophageal Cancer

In patients with esophageal cancer, adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA in combination with chemotherapy (cisplatin and 5-FU) compared to placebo plus chemotherapy (cisplatin and 5-FU) were: vomiting (7% vs. 5%), stomatitis (6% vs. 3.8%),

neutrophil count decreased (24.1% vs 17.3%), and white blood cell count decreased (9.2% vs. 4.9%).

Gastric Cancer

In patients with gastric cancer receiving KEYTRUDA plus chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity compared to placebo plus chemotherapy (fluoropyrimidine and platinum) were: anemia (12% vs. 10%), platelet count decreased (7% vs. 5%).

In patients with gastric cancer receiving KEYTRUDA plus trastuzumab and chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity compared to placebo plus trastuzumab and chemotherapy (fluoropyrimidine and platinum) were: vomiting (4.6% vs. 1.9%), anemia (14% vs.12%), decreased platelet count (14% vs.10%), and lymphopenia (13% vs.9%).

Renal Cell Carcinoma

In Combination with Axitinib (KEYNOTE-426)

The most common adverse events that occurred in at least 20% of previously untreated patients with RCC receiving KEYTRUDA and axitinib in KEYNOTE-426 were diarrhea, hypertension, fatigue, hypothyroidism, decreased appetite, palmar-plantar erythrodysaesthesia syndrome, nausea, ALT increased, AST increased, dysphonia, cough and constipation.

In KEYNOTE-426, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed in previously untreated patients with RCC receiving KEYTRUDA in combination with axitinib. 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 KEYTRUDA (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. *[See Dosage & Administration (2.1) and Warnings and Precautions (4)]*.

In Combination with Lenvatinib (KEYNOTE-581)

Table 8 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 8: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Sunitinib (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-581)

	KEYTRUDA + lenvatinib n=352		Sunitinib n=340	
Adverse Events	**All Grades* (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal Disorders				
Diarrhea	61	10	49	5
Nausea	36	2.6	33	0.6
Vomiting	26	3.4	20	1.5
Constipation	25	0.9	19	0
Abdominal pain	21	2.0	8	0.9
Vascular Disorders				
Hypertension	55	28	41	19
Endocrine Disorders				
Hypothyroidism	47	1.4	26	0
Metabolism and Nutrition Disorders				
Decreased appetite	40	4.0	31	1.5
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	30	0	4.1	0
Investigations				
Decreased weight	30	8	9	0.3
Renal and Urinary Disorders				
Proteinuria	30	8	13	2.9

Skin and Subcutaneous Tissue Disorders				
Rash	27	3.7	14	0.6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	28	1.4	15	0.3
Nervous System Disorders				
Headache	23	0.6	16	0.9

* Graded per NCI CTCAE v4.03

Endometrial Carcinoma

Table 9 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-775.

Table 9: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Doxorubicin or Paclitaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-775)

	KEYTRUDA + lenvatinib n=406		Doxorubicin or paclitaxel n=388	
Adverse Events*	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades† (%)**	**Grade 3-4 (%)**
Vascular Disorders				
Hypertension	64	37.9	5.2	2.3
Endocrine Disorders				
Hypothyroidism	57	1.2	0.8	0
Gastrointestinal Disorders				
Diarrhea	54	8	20	2.1
Nausea	50	3.4	46	1.3
Vomiting	37	2.7	21	2.3
Abdominal pain	20	2.5	14	1.3
Metabolism and Nutrition Disorders				
Decreased appetite	45	8‡	21	0.5
Investigations				

Decreased weight	34	10	6	0.3
Increased ALT	21	4.6	5	0.8
General Disorders and Administration Site Conditions				
Fatigue	33	5	28	3.1
Asthenia	24	6	24	3.9
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	31	1.7	8	0
Renal and Urinary Disorders				
Proteinuria	29	5	2.8	0.3
Infections				
Urinary tract infection	26	3.9	10	1.0
Nervous System Disorders				
Headache	25	0.5	9	0.3
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	23	0	0.5	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	21	2.7	0.8	0

* The median duration of study treatment was 7.6 months (range: 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day to 25.8 months) compared to 3.4 months (range: 1 day to 25.8 months) for chemotherapy.

† Graded per NCI CTCAE v4.03

‡ There was one Grade 5 (0.2%) reported.

Discontinuation of KEYTRUDA, lenvatinib or both due to an adverse reaction (Grades 1-4) occurred in 30% of patients; 15% KEYTRUDA, and 11% both drugs. The most common adverse reactions leading to discontinuation of KEYTRUDA were diarrhea, increased ALT, and intestinal obstruction (each 1.0%). Refer to the lenvatinib prescribing information for lenvatinib discontinuation information.

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 69% of patients; KEYTRUDA was interrupted in 50%, and both drugs were interrupted in 31% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were diarrhea (8%), increased ALT (3.9%),

hypertension (3.4%), increased AST (3.2%), decreased appetite (2.2%), fatigue (2.2%), urinary tract infection (2.2%), proteinuria (2.0%), and asthenia (2.0%). Refer to the lenvatinib prescribing information for lenvatinib interruption information.

In Combination with Chemotherapy (KEYNOTE-868)

In patients with endometrial carcinoma receiving KEYTRUDA plus chemotherapy (paclitaxel and carboplatin), adverse events were generally similar to those observed with KEYTRUDA alone or chemotherapy alone with the exception of rash maculo-papular (13% all Grades; 2% Grades 3-4).

Triple-Negative Breast Cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC

In patients with high-risk early-stage TNBC receiving KEYTRUDA in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment, adverse events occurring in at least 20% of the patients and at a higher incidence (≥5% difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued alone as adjuvant treatment were diarrhea (41% vs. 34%), rash (30% vs. 24%), pyrexia (28% vs. 19%), and decreased appetite (23% vs. 17%). Of these adverse events, Grade 3-4 events were diarrhea (3.2% vs. 1.8%), rash (1.8% vs. 0.3%), pyrexia (1.3% vs. 0.3%), and decreased appetite (0.9% vs. 0.3%).

KEYNOTE-355: Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC

In patients with TNBC receiving KEYTRUDA in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin), adverse events occurring in at least 20% of the patients and at a higher incidence (≥5% difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) were diarrhea (28% vs. 23%), decreased appetite (21% vs. 14%), and rash (20% vs. 12%). Of these adverse events, Grade 3-4 events were diarrhea (1.8% vs. 1.8%), decreased appetite (0.8% vs. 0.4%), and rash (0.8% vs. 0.0%).

Cervical Cancer

In patients with cervical cancer receiving KEYTRUDA plus CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]), adverse events occurring at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA plus CRT compared to placebo plus CRT was leukopenia (13% vs. 11%).

In patients with cervical cancer receiving KEYTRUDA plus chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab, adverse events occurring at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA plus chemotherapy with or without bevacizumab compared to placebo plus chemotherapy with or without bevacizumab were: anemia (30% vs. 27%), neutropenia (12% vs. 10%), thrombocytopenia (8% vs. 5%), asthenia (3.6% vs. 1.6%).

Biliary Tract Carcinoma

In patients with BTC receiving KEYTRUDA plus chemotherapy (gemcitabine and cisplatin), adverse events occurring at a higher incidence (≥5%) compared to placebo plus chemotherapy were pyrexia (26% vs. 20%), rash (17% vs. 9%), pruritus (15% vs. 10%) and hypothyroidism (9% vs. 2.6%). Of these adverse events, Grades 3-4 events were pyrexia (2.3% vs. 0.9%), rash (0.6% vs. 0.4%), pruritus (0.0% vs. 0.0%) and hypothyroidism (0.2% vs. 0.0%).

7.2 Postmarketing Experience

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

Musculoskeletal and connective tissue disorders: arthritis
Eye disorders: Vogt-Koyanagi-Harada syndrome
Immune system disorders: hemophagocytic lymphohistiocytosis
Nervous system disorders: optic neuritis.

8. OVERDOSAGE

There is no information on overdosage with KEYTRUDA. The maximum tolerated dose of KEYTRUDA has not been determined. In clinical trials, patients received up to 10 mg/kg with a similar safety profile to that seen in patients receiving 2 mg/kg.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

9. CLINICAL STUDIES

Melanoma

KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab

The efficacy of KEYTRUDA was investigated in KEYNOTE-006, a multicenter, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were randomized (1:1:1) to receive KEYTRUDA at a dose of 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Randomization was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study excluded patients with autoimmune disease or those receiving immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with KEYTRUDA 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 tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter.

Of the 834 patients in KEYNOTE-006, 60% were male, 44% were ≥65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-six percent had no prior systemic therapies and thus received study therapy as first-line treatment whereas 34% had one prior therapy and thus received study therapy as second-line treatment. Thirty-one percent had an ECOG PS of 1 and 69% had an ECOG PS of 0. Eighty percent of

patients were PD-L1 positive (PD-L1 membrane expression in ≥1% of tumor and associated immune cells as assessed prospectively by an immunohistochemistry assay with the 22C3 anti-PD-L1 antibody) and 18% were PD-L1 negative. Sixty-five percent of patients had M1c stage, 32% had elevated LDH and 9% had brain metastases. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumors, 139 (46%) were previously treated with a BRAF inhibitor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were overall survival (OS) and progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumors [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 10 summarizes key efficacy measures.

Table 10: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks in patients with ipilimumab naïve advanced melanoma in KEYNOTE-006

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab n=278
OS*			
Number (%) of patients with event	92 (33%)	85 (30%)	112 (40%)
Hazard ratio† (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value‡	0.00358	0.00052	---
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)	Not reached (13, NA)
PFS§ by IRO¶			
Number (%) of patients with event	157 (57%)	157 (56%)	188 (68%)
Hazard ratio† (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value‡	<0.00001	<0.00001	---
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)

Best overall response§ by IRO¶			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%
Response duration# by IRO¶			
Median in months (range)	Not reached (2.0+, 22.8+)	Not reached (1.8+, 22.8)	Not reached (1.1+, 23.8+)
% ongoing at 12 monthsÞ	79%	75%	79%

* Based on second interim analysis

† Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

‡ Based on stratified Log rank test

§ Based on first interim analysis

¶ IRO=Independent radiology plus oncologist review using RECIST 1.1

Based on patients with a best overall response as confirmed complete or partial response from the final analysis

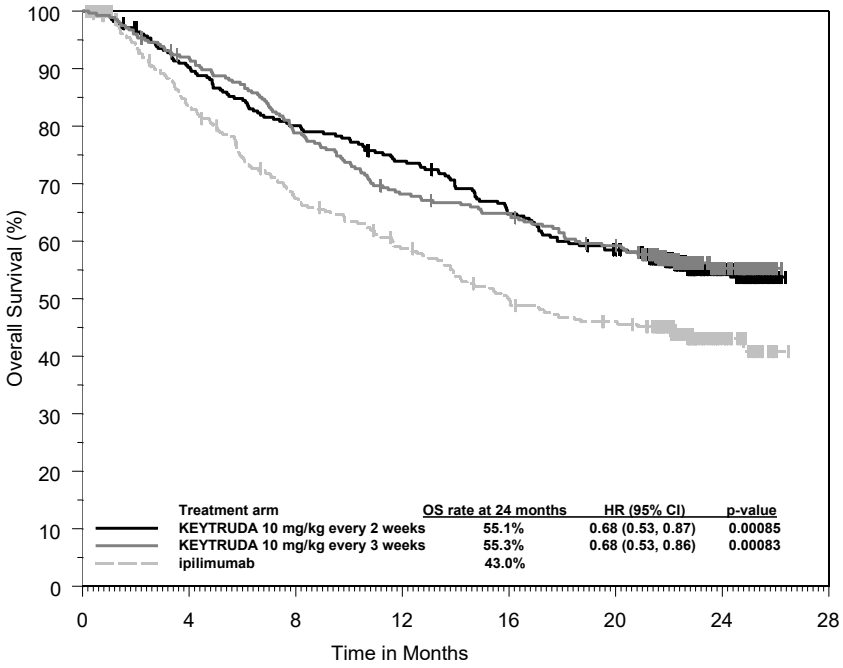
Þ Based on Kaplan-Meier estimates

NA = not available

The final analysis was performed after all patients had at least 21 months of follow-up. The final OS analysis was performed after 383 patient events (119 for KEYTRUDA 10 mg/kg every 3 weeks, 122 for KEYTRUDA 10 mg/kg every 2 weeks and 142 for ipilimumab). The OS HRs vs. ipilimumab were 0.68 (95% CI: 0.53, 0.86; p<0.001) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.68 (95% CI: 0.53, 0.87; p<0.001) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. The OS rate at 18 months and 24 months were 62% and 55% respectively for KEYTRUDA 10 mg/kg every 3 weeks, 60% and 55% respectively for KEYTRUDA 10 mg/kg every 2 weeks, and 47% and 43% respectively for ipilimumab. At the final analysis, a long-term PFS analysis was performed based on 566 patient events (183 for KEYTRUDA 10 mg/kg every 3 weeks, 181 for KEYTRUDA 10 mg/kg every 2 weeks and 202 for ipilimumab). The PFS HRs vs. ipilimumab were 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. (See Figures 1 and 2.) The percentage of

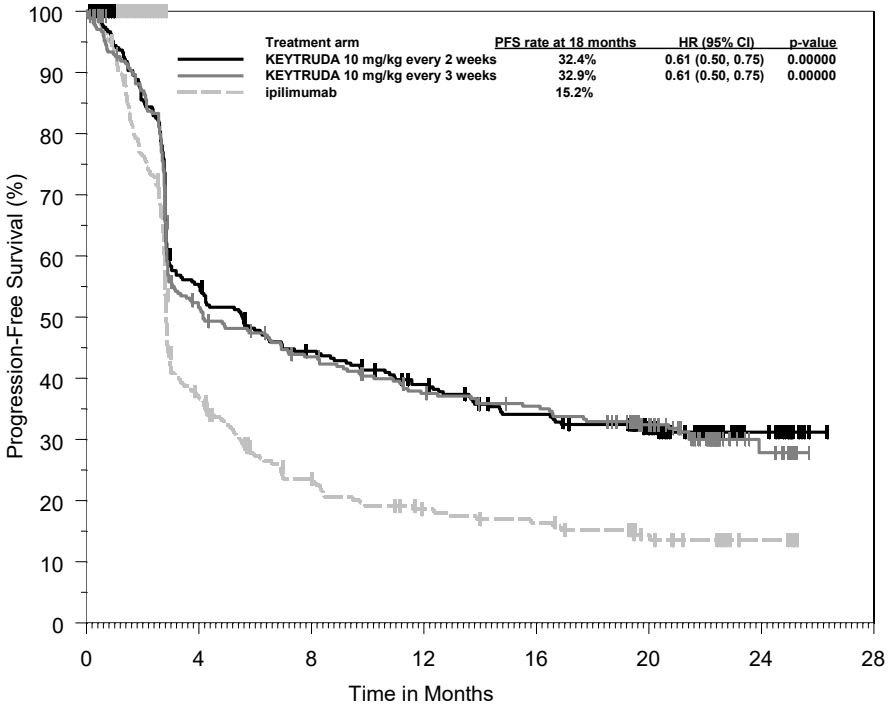
responders with an ongoing response at 18 months was 68% for KEYTRUDA 10 mg/kg every 3 weeks, 71% for KEYTRUDA 10 mg/kg every 2 weeks and 70% for ipilimumab.

Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



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

Figure 2: Kaplan-Meier curve for progression-free survival (based on IRO) by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk								
KEYTRUDA 10 mg/kg every 2 weeks:	279	148	116	98	82	52	16	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	136	111	91	84	60	13	0
ipilimumab:	278	88	48	34	29	16	5	0

Sub-population analysis by BRAF mutation status

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment. The PFS hazard ratios (HRs) (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.61 (95% CI: 0.49, 0.76) for BRAF wild type, 0.52 (95% CI: 0.35, 0.78) for BRAF mutant without prior BRAF treatment, and 0.76 (95% CI: 0.51, 1.14) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.68 (95% CI: 0.52, 0.88) for BRAF wild type, 0.70 (95% CI: 0.40, 1.22) for BRAF mutant without prior BRAF treatment, and 0.66 (95% CI: 0.41, 1.04) for BRAF mutant with prior BRAF treatment. ORR for pooled KEYTRUDA vs. ipilimumab was 38% vs. 14% for BRAF wild type, 41% vs. 15% for BRAF mutant without prior BRAF treatment, and 24% vs. 10% for BRAF mutant with prior BRAF treatment.

Sub-population analysis by PD-L1 status

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive vs. PD-L1 negative. The PFS HRs (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.44, 0.65) for PD-L1 positive patients and 0.87 (95% CI: 0.58, 1.30) for PD-L1 negative patients. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.63 (95% CI: 0.50, 0.80) for PD-L1 positive patients and 0.76 (95% CI: 0.48, 1.19) for PD-L1 negative patients.

KEYNOTE-002: Controlled trial in melanoma patients previously-treated with ipilimumab

The efficacy of KEYTRUDA was investigated in KEYNOTE-002, a multicenter, controlled study for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomized (1:1:1) to receive KEYTRUDA at a dose of 2 (n=180) or 10 mg/kg (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; 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 (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, hepatitis B or hepatitis C infection.

Patients were treated with KEYTRUDA 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 tumor 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 or 10 mg/kg of KEYTRUDA every 3 weeks in a double-blind fashion.

Of the 540 patients in KEYNOTE-002, 61% were male, 43% were ≥65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent of patients had M1c stage, 73% had at least two and 32% had three or more prior systemic therapies

for advanced melanoma. Forty-five percent had an ECOG PS of 1, 40% had elevated LDH and 23% had a BRAF mutated tumor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1) and OS. Secondary efficacy outcome measures were PFS (as assessed by Investigator using RECIST 1.1), ORR and response duration. Table 11 summarizes key efficacy measures in patients previously treated with ipilimumab. OS data were not mature at the time of the PFS analysis. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA.

Table 11: Response to KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks in patients with unresectable or metastatic melanoma 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
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‡	0.117	0.011è	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
PFS§ by IRO¶			
Number (%) of patients with event	129 (72%)	126 (70%)	155 (87%)
Hazard ratio† (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
p-Value‡	<0.0001	<0.0001	---

Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
Mean in months (95% CI) [#]	5.4 (4.7, 6.0)	5.8 (5.1, 6.4)	3.6 (3.2, 4.1)
PFS[§] by INV[Þ]			
Number (%) of patients with event	122 (68%)	112 (62%)	157 (88%)
Hazard ratio[†] (95% CI)	0.49 (0.38, 0.62)	0.41 (0.32, 0.52)	---
p-Value[‡]	<0.0001	<0.0001	---
Median in months (95% CI)	3.7 (2.9, 5.4)	5.4 (3.8, 6.8)	2.6 (2.4, 2.8)
Mean in months (95% CI) [#]	5.8 (5.2, 6.4)	6.5 (5.8, 7.1)	3.7 (3.2, 4.1)
Best overall response[§] by IRO[¶]			
ORR % (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%
Response duration[ß] by IRO[¶]			
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[à]	73%	79%	Not reached[ð]

* Based on final analysis

† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

‡ Based on stratified Log rank test

§ Based on second interim analysis

¶ IRO=Independent radiology plus oncologist review using RECIST 1.1

Restricted mean progression-free survival time based on follow-up of 12 months

Þ INV=Investigator assessment using RECIST 1.1

ß Based on patients with a best overall response as confirmed complete or partial response from the final analysis

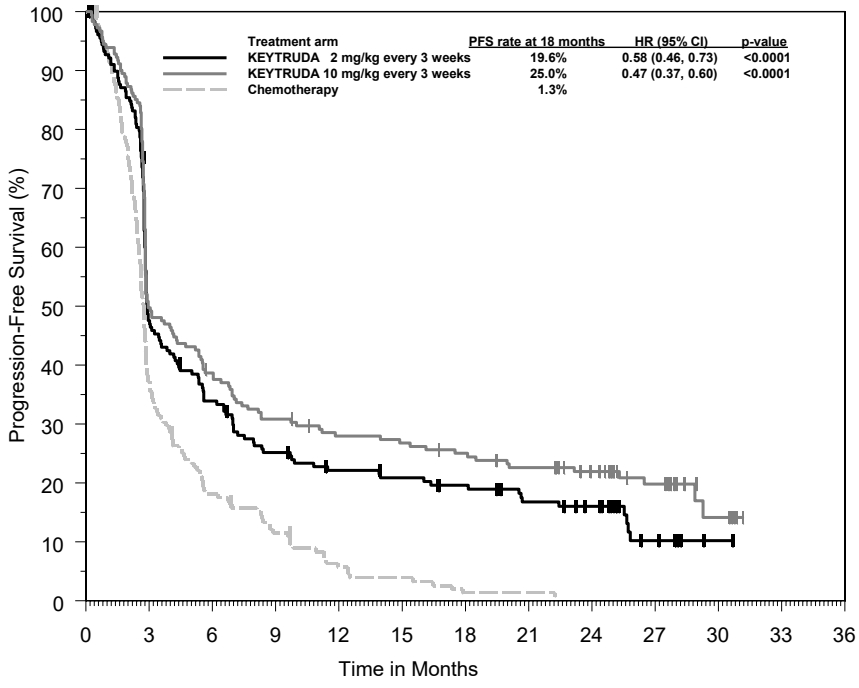
à Based on Kaplan-Meier estimates

è Not statistically significant after adjustment for multiplicity

ð The maximum follow-up for ongoing patients in the chemotherapy arm is 11.3 months; patients continue to be followed

At the final analysis, a long-term PFS analysis was performed based on 466 PFS events (150 for KEYTRUDA 2 mg/kg every 3 weeks; 144 for KEYTRUDA 10 mg/kg every 3 weeks; and 172 for chemotherapy). The PFS HRs vs. chemotherapy were 0.58 (95% CI: 0.46, 0.73) for patients treated with KEYTRUDA 2 mg/kg every 3 weeks and 0.47 (95% CI: 0.37, 0.60 for patients treated with KEYTRUDA 10 mg/kg every 3 weeks (Figure 3).

Figure 3: Kaplan-Meier Curve for Progression Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-002 (Intent To Treat Population)



Number at Risk

KEYTRUDA 2 mg/kg every 3 weeks:	180	59	36	29	19	1	0
KEYTRUDA 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

The efficacy of KEYTRUDA was also investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 276 patients from two defined cohorts of KEYNOTE-001, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, a BRAF or MEK

inhibitor) and another which included patients naïve to treatment with ipilimumab. Patients were randomized to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. Patients were treated with KEYTRUDA 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 of KEYTRUDA 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 of patients had M1c stage and 8% had a history of brain metastases. Seventy-eight percent of patients had at least two and 35% had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population.

Of the 51 patients receiving 2 mg/kg of KEYTRUDA 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 of patients had M1c stage and 2% had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 39% of the study population.

The primary efficacy outcome measure was ORR as assessed by independent review using confirmed responses and 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. Tumor response was assessed at 12-week intervals. Table 12 summarizes key efficacy measures in patients, previously treated or naïve to treatment with ipilimumab, receiving KEYTRUDA at a dose of 2 mg/kg based on a minimum follow-up time of 30 months for all patients.

Table 12: Response to KEYTRUDA 2 mg/kg every 3 weeks in patients with unresectable or metastatic melanoma in KEYNOTE-001

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks in patients previously treated with ipilimumab n=89	KEYTRUDA 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab n=51
Best Overall Response* by IRO†		
ORR %, (95% CI)	26% (17, 36)	35% (22, 50)
Disease Control Rate %‡	48%	49%
Complete response	7%	12%
Partial response	19%	24%
Stable disease	20%	14%
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 = Independent radiology plus oncologist review 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 of KEYTRUDA every 3 weeks were similar to those seen in patients who received 2 mg/kg of KEYTRUDA every 3 weeks.

KEYNOTE-716: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage IIB or IIC melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-716, a multicenter, randomized, double-blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma. A total of 976 patients were randomized (1:1) to receive 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 (n=487) or placebo (n=489) for up to one year, until disease recurrence, or until unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 8th edition (AJCC) T stage. Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients underwent imaging every 6 months for 1 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.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; and 93% ECOG PS of 0 and 7% ECOG PS of 1. 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 randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occured 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 these analyses.

The trial initially demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the pembrolizumab arm compared with placebo. Results reported from the pre-specified interim analysis for RFS with a median follow-up of 14.3 months are summarized in Table 13. Results reported from the pre-specified interim analysis for DMFS with a median follow-up of 26.9 months are summarized in Table 13 and Figure 5.

Table 13: 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%)
RFS rate at 18 months	85.8%	77%
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.65 (0.46, 0.92)	
p-Value (stratified log-rank)	0.00658	
DMFS		
Number (%) of patients with event	63 (13%)	95 (19%)
DMFS rate at 24 months	88.1%	82.2%
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.64 (0.47, 0.88)	
p-Value (stratified log-rank)	0.00292	

* Based on the stratified Cox proportional hazard model

NR=not reached

A pre-specified sensitivity analysis of RFS that included new primary melanomas was consistent with the primary RFS analysis, with an HR of 0.64 (95% CI: 0.46, 0.88).

A pre-specified final analysis for RFS was performed with a median follow-up of 20.5 months (range: 4.6 to 32.7 months). At the time of this analysis, the hazard ratio in patients randomized to pembrolizumab versus patients randomized to placebo was 0.61 (95% CI: 0.45, 0.82) with 72/487 (14.8%) events and 115/489 (23.5%), respectively. Updated RFS results with a median follow-up of 26.9 months were consistent with the final analysis for RFS for patients randomized to the pembrolizumab arm compared with

placebo (HR 0.64; 95% CI: 0.50, 0.84). These efficacy results are summarized in Figure 4.

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716 (Intent to Treat Population)

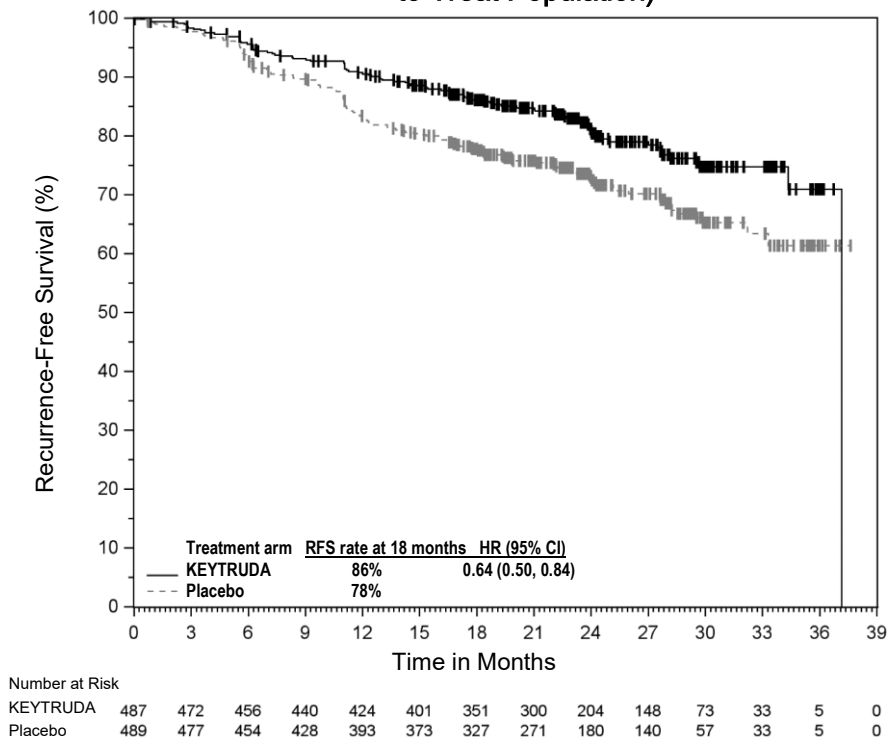
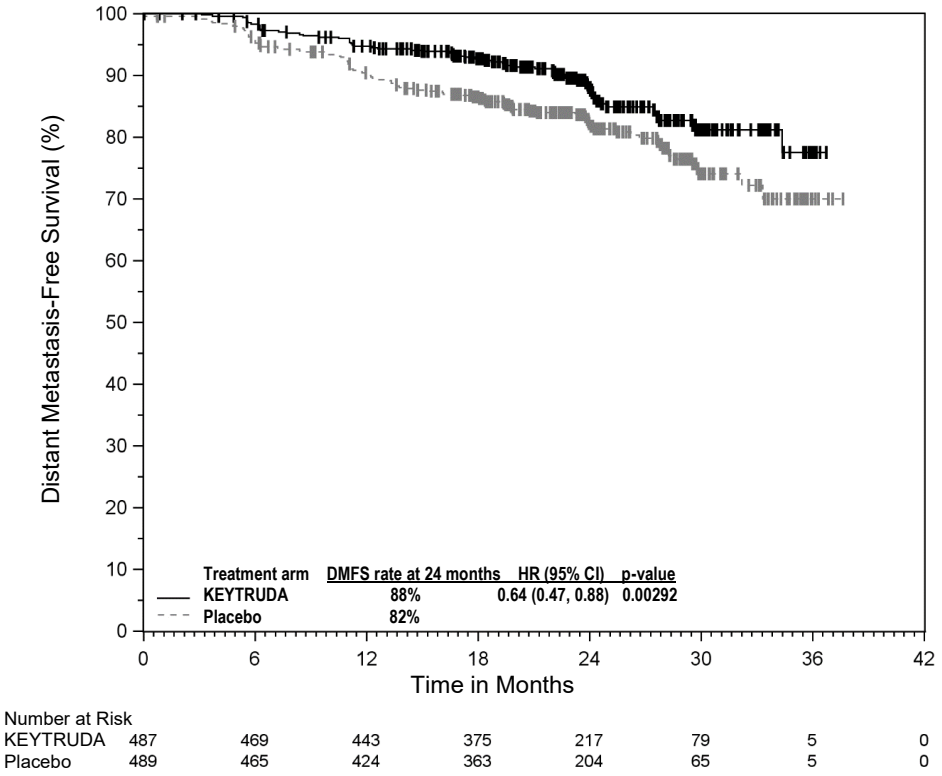


Figure 5: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE-716 (Intent to Treat Population)



KEYNOTE-054: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage III melanoma

The efficacy of KEYTRUDA was evaluated in KEYNOTE-054, a multicenter, randomized double-blind, placebo-controlled trial in patients with completely resected stage IIIA (> 1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1019 patients were randomized (1:1) to receive KEYTRUDA 200 mg every three weeks (n=514) or placebo (n=505), for up to one year, until disease recurrence, or until unacceptable toxicity. Randomization was stratified by 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. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. 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.

Among the 1019 patients, the baseline characteristics were: median age of 54 years (25% age 65 or older); 62% male; 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; 84% had PD-L1 positive melanoma with tumor proportion score (TPS ≥1%) according to an investigational use only (IUO) assay.

The primary efficacy outcome measures were investigator-assessed RFS in the whole population and in the population with PD-L1 positive tumors. 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 trial initially demonstrated a statistically significant improvement in RFS (HR 0.57; 98.4% CI: 0.43, 0.74; p-Value < 0.0001) for patients randomized to the KEYTRUDA arm compared with placebo at its pre-specified interim analysis. RFS efficacy results with a median follow-up time of 16.0 months are summarized in Table 14 and Figure 6. DMFS efficacy results with a median follow-up time of 45.5 months are summarized in Table 14 and Figure 7.

Table 14: 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%)
RFS rate at 6 months	82%	73%
Median in months (95% CI)	NR (NR, NR)	20.4 (16.2, NR)
Hazard ratio* (98% CI)	0.57 (0.43, 0.74)	
p-Value (stratified log-rank)	<0.0001	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
DMFS rate at 42 months	65%	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 (stratified log-rank)	< 0.0001

* Based on the stratified Cox proportional hazard model

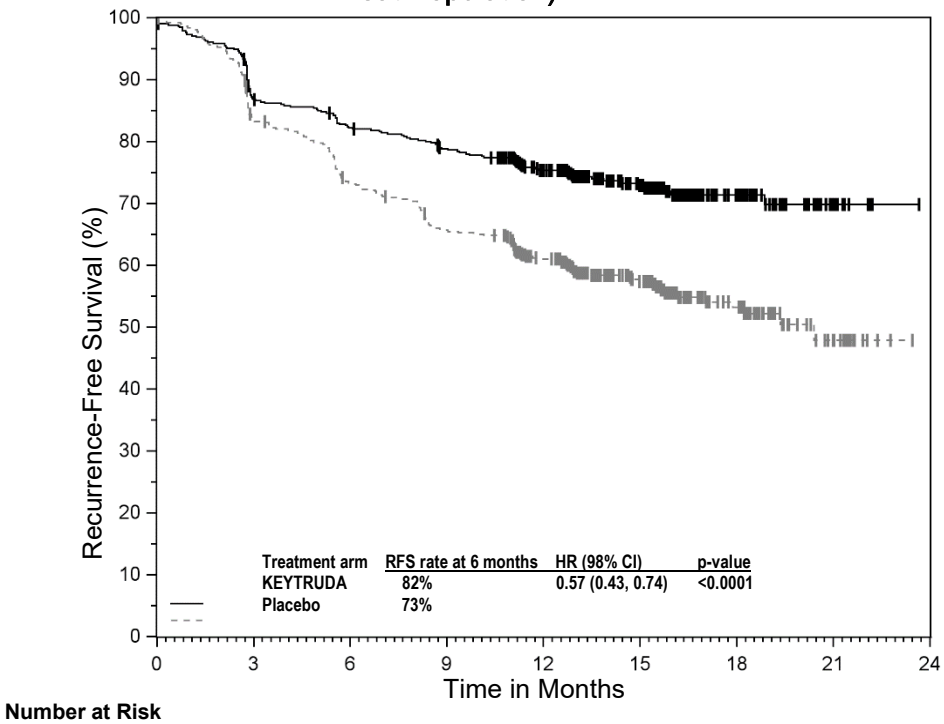
NR = not reached

For patients in the whole population, the RFS rate at 42 months was 60% in the KEYTRUDA arm and 41% in the placebo arm (HR was 0.59 [95% CI: 0.49, 0.70]).

For patients with PD-L1 positive tumors, the RFS rate at 42 months was 61% in the KEYTRUDA arm and 44% in the placebo arm (HR was 0.59 (95% CI: 0.49, 0.73)). Additionally, pre-defined subgroup analyses were performed in patients whose tumors were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression or BRAF mutation status. The RFS HR for KEYTRUDA was 0.46 (95% CI: 0.27, 0.77) for patients with PD-L1 negative tumors. The RFS HR was 0.52 (95% CI: 0.40, 0.66) for patients with BRAF mutation positive tumors, and 0.67 (95% CI: 0.51, 0.88) for patients with BRAF mutation negative tumors.

For patients with PD-L1 positive tumors, the DMFS rate at 42 months was 67% in the KEYTRUDA arm and 52% in the placebo arm (HR was 0.61 (95% CI: 0.49, 0.76); p <0.0001). Additionally, pre-defined subgroup analyses were performed in patients whose tumors were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression or BRAF mutation status. The DMFS HR for KEYTRUDA was 0.49 (95% CI: 0.28, 0.83) for patients with PD-L1 negative tumors. The DMFS HR was 0.51 (95% CI: 0.39, 0.68) for patients with BRAF mutation positive tumors, and 0.73 (95% CI: 0.55, 0.98) for patients with BRAF mutation negative tumors.

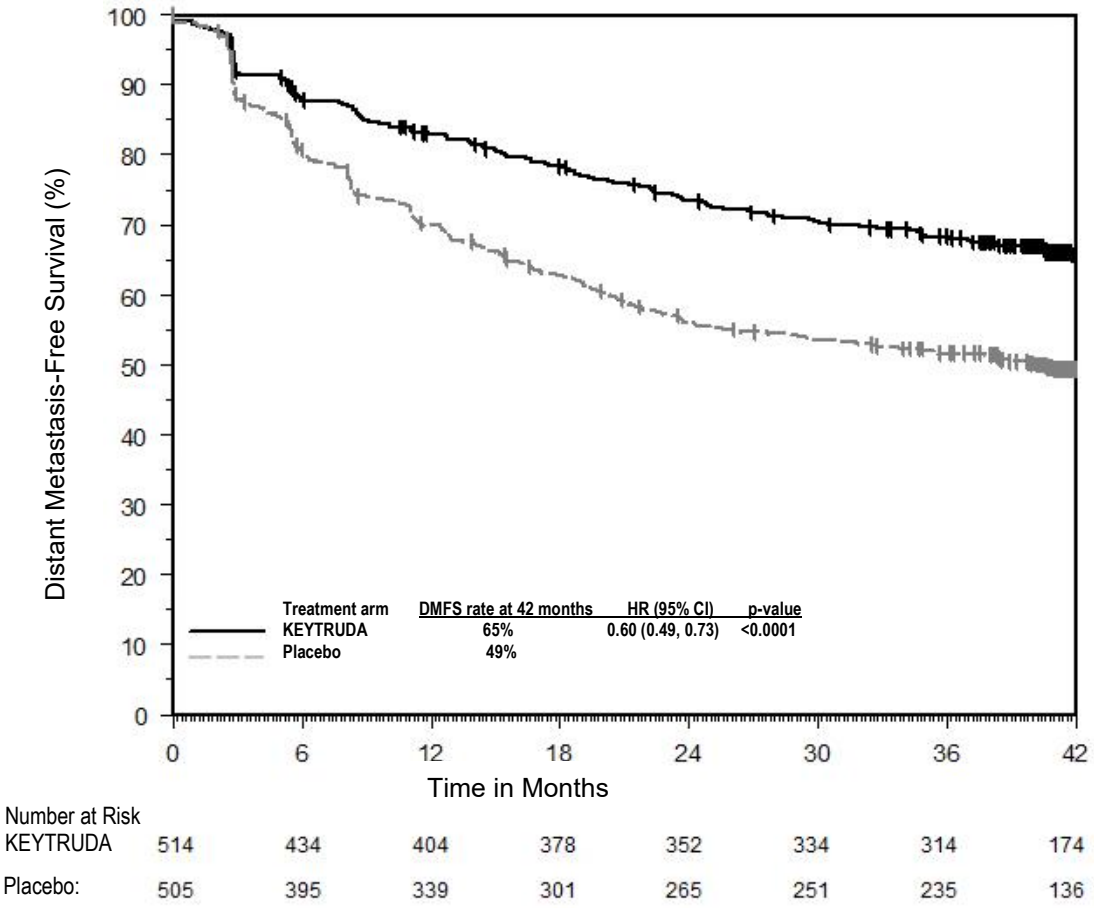
Figure 6: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (Intent to Treat Population)



Number at Risk

KEYTRUDA	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

Figure 7: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE-054 (Intent to Treat Population)



Non-Small Cell Lung Carcinoma

KEYNOTE-189: Controlled trial of combination therapy in non-squamous NSCLC patients naïve to treatment

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, active-controlled, double-blind trial, KEYNOTE-189. Key eligibility criteria were metastatic non-squamous NSCLC, no prior systemic treatment for metastatic NSCLC, and 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. Patients were randomized (2:1) to receive one of the following regimens:

- KEYTRUDA 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 KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks.

- 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.

Treatment with KEYTRUDA continued until RECIST 1.1-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 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 KEYTRUDA could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of tumor 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 KEYTRUDA as monotherapy.

Among the 616 patients in KEYNOTE-189 (410 patients in the KEYTRUDA combination arm and 206 in the placebo plus chemotherapy arm), 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% with PD-L1 TPS <1%; and 18% with treated or untreated brain metastases at baseline. A total of 67 patients in the placebo plus chemotherapy arm crossed over to receive monotherapy KEYTRUDA at the time of disease progression and 18 additional patients received a checkpoint inhibitor as subsequent therapy.

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 median follow-up time was 10.5 months (range: 0.2-20.4 months). Table 15 summarizes key efficacy measures.

Table 15: Response to KEYTRUDA, pemetrexed, and platinum chemotherapy in patients with non-squamous NSCLC in KEYNOTE-189

Endpoint	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=410	Placebo + Pemetrexed + Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	Not reached (NA, NA)	11.3 (8.7, 15.1)
PFS		
Number (%) of patients with event	245 (60%)	166 (81%)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
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	
Response duration		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)
% with duration ≥6 months¶	81%	63%
% with duration ≥9 months¶	59%	44%

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best overall 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

NA = not available

The final OS analysis was performed at a median duration of follow-up of 18.8 months after 421 patient events (258 for the KEYTRUDA combination arm and 163 for the placebo plus chemotherapy arm). Median OS was 22.0 months (95% CI: 19.5, 24.5) for the KEYTRUDA combination arm and 10.6 months (95% CI: 8.7, 13.6) for the placebo plus chemotherapy arm. The OS HR was 0.56 (95% CI: 0.46, 0.69; p<0.00001). At final analysis, a PFS analysis was performed based on 534 patient events (337 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). The median PFS was 9.0 months (95% CI: 8.1, 10.4) for the KEYTRUDA combination arm and 4.9 months (95% CI: 4.7, 5.5) for the placebo plus chemotherapy arm. The PFS HR was 0.49 (95% CI: 0.41, 0.59, p<0.00001). See Figures 8 and 9.

The ORR at the final analysis was 48% for the KEYTRUDA combination arm and 20% for the placebo plus chemotherapy arm. The median duration of response was 12.5 months (range 1.1+, 34.9+) for the KEYTRUDA combination arm and 7.1 months (range 2.4, 27.8+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 53% at 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 27% in patients who received placebo plus chemotherapy.

Figure 8: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

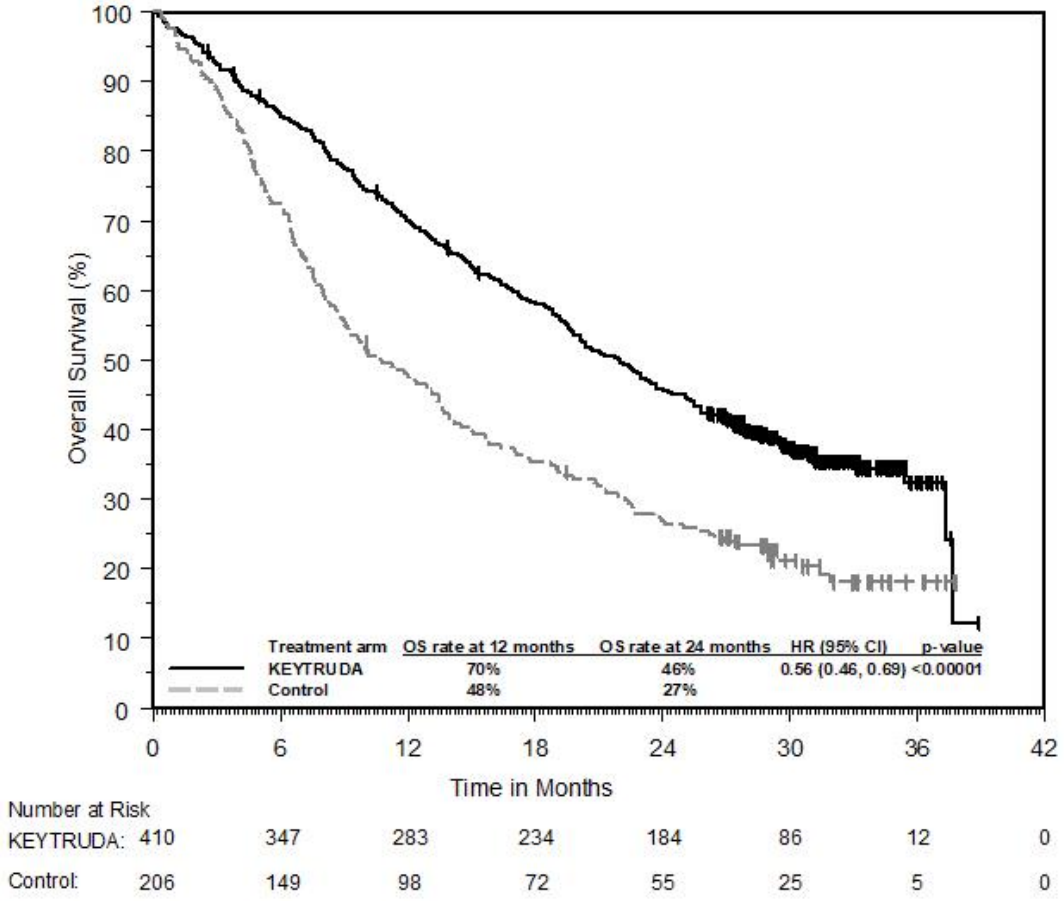


Figure 9: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)

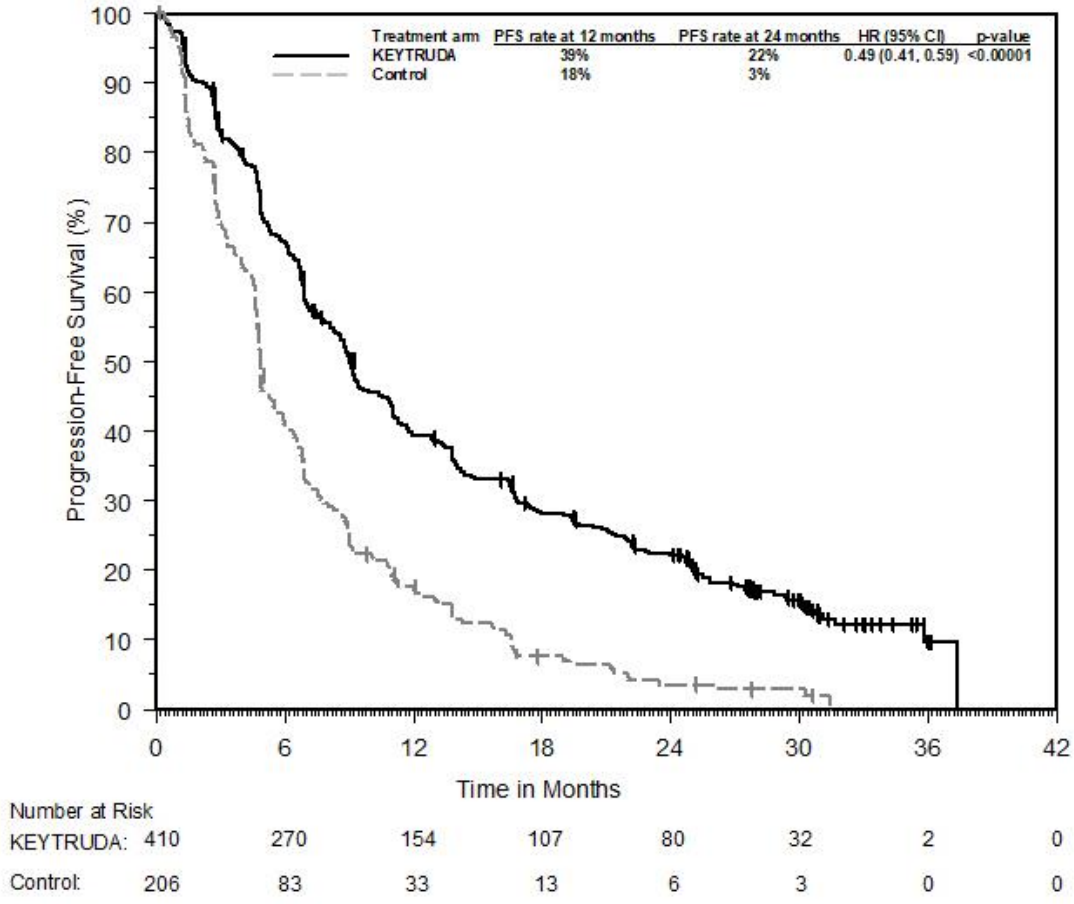


Table 16: Efficacy results by PD-L1 Expression in KEYNOTE-189

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)	0.59 (0.38, 0.92)		0.55 (0.34, 0.90)		0.42 (0.26, 0.68)	
PFS Hazard ratio* (95% CI)	0.75 (0.53, 1.05)		0.55 (0.37, 0.81)		0.36 (0.25, 0.52)	

* Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model

At final analysis in study KEYNOTE-189, in patients who had PD-L1 TPS <1% the OS HR was 0.51 [95% CI 0.36, 0.71] and the PFS HR was 0.67 [95% CI 0.49, 0.93] for the KEYTRUDA combination arm vs. the placebo plus chemotherapy arm; in patients who had PD-L1 TPS 1-49% the OS HR was 0.66 [95% CI 0.46, 0.96] and the PFS HR was 0.53 [95% CI 0.38, 0.74] for the KEYTRUDA combination arm vs. the placebo plus chemotherapy arm; in patients who had PD-L1 TPS ≥50% the OS HR was 0.59 [95% CI 0.40, 0.86] and the PFS HR was 0.35 [95% CI 0.25, 0.49] for the KEYTRUDA combination arm vs. the placebo plus chemotherapy arm.

Patient-reported outcomes were assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13. Exploratory analyses of patients receiving pembrolizumab combination therapy showed stable EORTC QLQ-C30 Global Health Status/QoL at Week 12 and Week 21 vs declines in patients receiving placebo plus chemotherapy. There was a trend toward a prolonged time to deterioration in the EORTC QLQ-LC13/QLQ-C30 endpoint of cough, dyspnea or chest pain observed for patients receiving pembrolizumab combination therapy.

KEYNOTE-407: Controlled trial of combination therapy in squamous NSCLC patients naïve to treatment

The efficacy of KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumor 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. Randomization was stratified by tumor 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 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 nab-paclitaxel 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 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 KEYTRUDA or placebo continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (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. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year.

Patients in the placebo arm were offered KEYTRUDA as monotherapy 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 major efficacy outcome measures were progression-free survival and objective response rate (ORR) as assessed by BICR using RECIST 1.1 and overall survival. An additional efficacy outcome measure was duration of response as assessed by BICR using RECIST 1.1.

A total of 559 patients were randomized: 278 patients to the KEYTRUDA arm and 281 to the placebo arm. 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 tumor PD-L1 expression TPS <1% [negative]; 19% were from the East Asian region; and 60% received paclitaxel.

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 17).

Table 17: Efficacy Results in KEYNOTE-407

Endpoint	KEYTRUDA Carboplatin Paclitaxel/Nab-paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-paclitaxel n=281
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NA)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value (stratified log rank)	0.0008	
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 (stratified log rank)	<0.0001	
Overall Response Rate		
ORR†	58%	38%
(95% CI)	(52, 64)	(33, 44)
Response Duration		
Median duration of response in months (range)	7.7 (1.1+, 14.7+)	4.8 (1.3+, 15.8+)
% with duration ≥ 6 months‡	62%	40%

* Based on the stratified Cox proportional hazard model

† At the initial interim analysis (n=101 for KEYTRUDA combination therapy, n=102 for placebo), a statistically significant difference was observed; ORR was 58% [95% CI (48, 68)] and 35% [95% CI (26, 45)] for placebo, p=0.0004

‡ Based on Kaplan-Meier estimation

NA = not available

The final OS analysis was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). Median OS was 17.1 months (95% CI: 14.4, 19.9) for the KEYTRUDA combination arm and 11.6 months (95% CI: 10.1, 13.7) for the

placebo plus chemotherapy arm. The OS HR was 0.71 (95% CI: 0.58, 0.88; p=0.0006). At final analysis, a PFS analysis was performed based on 469 patient events (217 for the KEYTRUDA combination arm and 252 for the placebo plus chemotherapy arm). The median PFS was 8.0 months (95% CI: 6.3, 8.4) for the KEYTRUDA combination arm and 5.1 months (95% CI: 4.3, 6.0) for the placebo plus chemotherapy arm. The PFS HR was 0.57 (95% CI: 0.47, 0.69, p<0.0001). See Figures 10 and 11.

The ORR at the final analysis was 63% for the KEYTRUDA combination arm and 38% for the placebo plus chemotherapy arm. The median duration of response was 8.8 months (range 1.3+, 28.4+) for the KEYTRUDA combination arm and 4.9 months (range 1.3+, 28.3+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 64% and 38% at 6 and 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 44% and 25% in patients who received placebo plus chemotherapy.

Figure 10: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

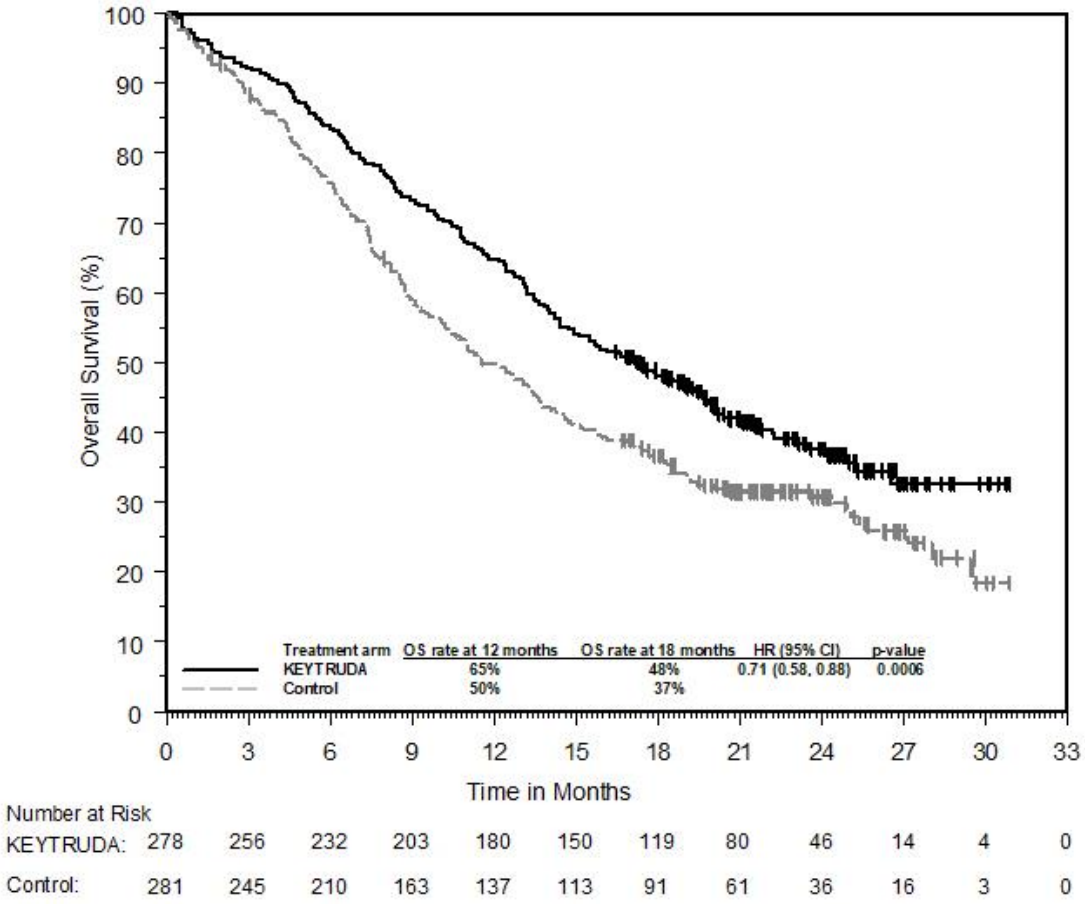


Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407

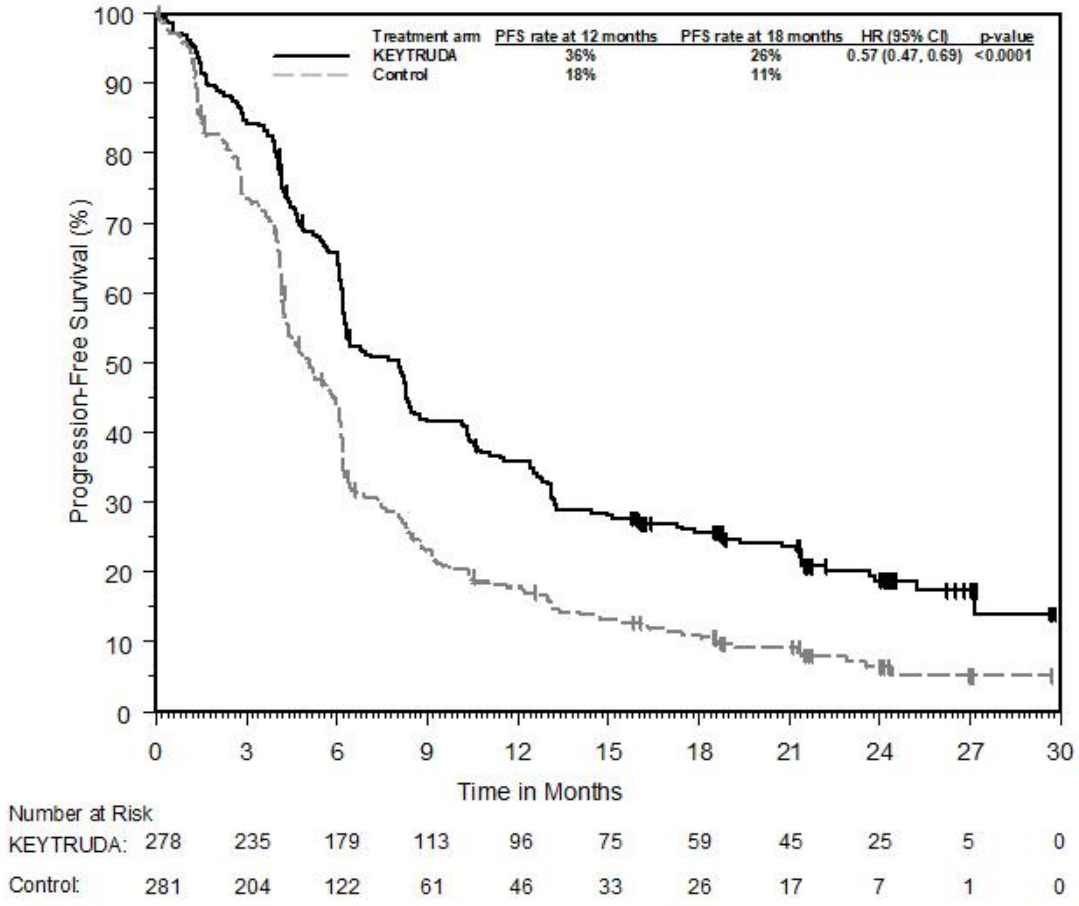


Table 18: Efficacy results by PD-L1 Expression in KEYNOTE-407

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)	0.61 (0.38, 0.98)		0.57 (0.36, 0.90)		0.64 (0.37, 1.10)	
PFS Hazard ratio* (95% CI)	0.68 (0.47, 0.98)		0.56 (0.39, 0.80)		0.37 (0.24, 0.58)	

* Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model

At final analysis in study KEYNOTE-407, in patients who had PD-L1 TPS <1% the OS HR was 0.79 [95% CI 0.56, 1.11] and the PFS HR was 0.67 [95% CI 0.49, 0.91] for the KEYTRUDA combination arm vs. the placebo plus chemotherapy arm; in patients who had PD-L1 TPS 1-49% the OS HR was 0.59 [95% CI 0.42, 0.84] and the PFS HR was 0.52 [95% CI 0.38, 0.71] for the KEYTRUDA combination arm vs. the placebo plus chemotherapy arm; in patients who had PD-L1 TPS ≥ 50% the OS HR was 0.79 [95% CI 0.52, 1.21] and the PFS HR was 0.43 [95% CI 0.29, 0.63] for the KEYTRUDA combination arm vs. the placebo plus chemotherapy arm.

KEYNOTE-024: Controlled trial of NSCLC patients naïve to treatment

The efficacy of KEYTRUDA was investigated in KEYNOTE-024, a multicenter, randomized, controlled trial. Key eligibility criteria were metastatic NSCLC, PD-L1 expression TPS of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx™ Kit, and no prior systemic treatment for metastatic NSCLC. 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. Patients were randomized (1:1) to receive KEYTRUDA 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. Non-squamous patients could receive pemetrexed maintenance). Patients were treated with KEYTRUDA 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. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 9 weeks. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, 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 19 summarizes key efficacy measures for the entire ITT population.

Table 19: 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%)
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	44 (29%)	64 (42%)
Hazard ratio† (95% CI)	0.60 (0.41, 0.89)	
p-Value‡	0.005	
Median in months (95% CI)	Not reached (NA, NA)	Not reached (9.4, NA)
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%

* Assessed by BICR using RECIST 1.1

† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

‡ Based on stratified Log rank test

§ Based on patients with a best overall response as confirmed complete or partial response

¶ Based on Kaplan-Meier estimates;

NA = not available

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86; p=0.002). See Figure 13.

Figure 12: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

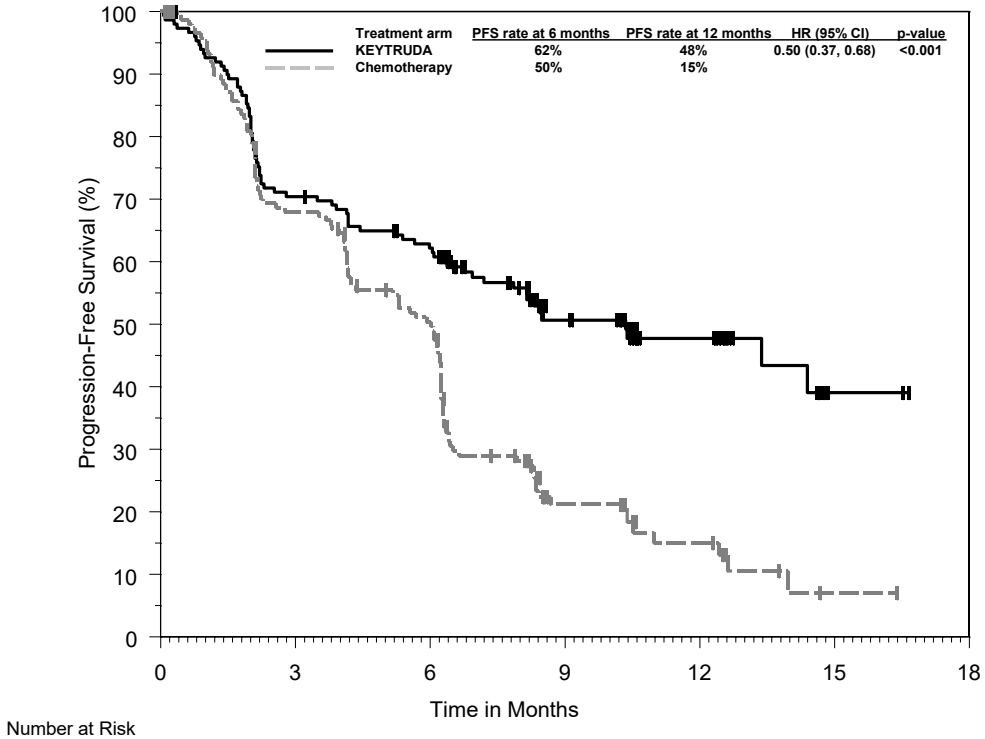
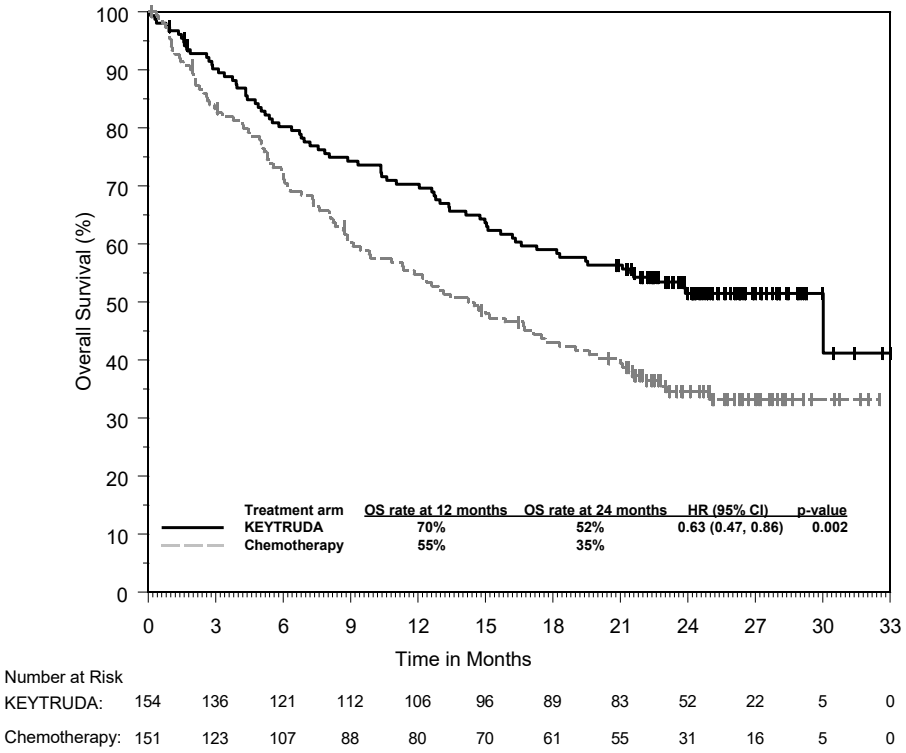


Figure 13: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



The improved benefit as assessed by PFS, OS, ORR, and response duration for KEYTRUDA as compared to chemotherapy in the population studied was associated with improvements in health-related quality of life (HRQoL). The change from baseline to Week 15 showed a meaningful improvement in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 global health status/QoL score for patients receiving KEYTRUDA compared to chemotherapy (difference in LS means = 7.82; 95% CI: 2.85, 12.79; two-sided p=0.002). The time to deterioration in the EORTC QLQ-LC13 composite endpoint of cough, dyspnea, and chest pain was prolonged for patients receiving KEYTRUDA compared to chemotherapy (HR = 0.66; 95% CI: 0.44, 0.97; two-sided p=0.029), where deterioration is defined as a confirmed 10-point or greater score decrease from baseline in any one of these three symptoms.

KEYNOTE-010: Controlled trial of NSCLC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, randomized, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted

therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by clinical trial assay version of 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. Patients were randomized (1:1:1) to receive 2 mg/kg (n=344) or 10 mg/kg (n=346) of KEYTRUDA every 3 weeks or 75 mg/m^2 of docetaxel every 3 weeks (n=343). Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 9 weeks.

Among the 1033 patients in KEYNOTE-010, baseline characteristics were: 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%); M1 (91%); brain metastases (15%); and the incidence of genomic aberrations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%), or two or more (29%) prior therapies.

The primary efficacy outcome measures were OS and PFS as assessed by an independent review committee using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 20 summarizes key efficacy measures for the entire ITT population (TPS ≥1%) and for the subgroup of patients with TPS ≥50%. Kaplan-Meier curves for OS (TPS ≥1% and TPS ≥50%) are shown in Figures 14 and 15.

Table 20: Response to KEYTRUDA 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks	KEYTRUDA 10 mg/kg 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	172 (50%)	156 (45%)	193 (56%)

Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS‡			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value†	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall response rate‡			
ORR %§ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response duration‡,¶,#			
Median in months (range)	Not reached (0.7+, 20.1+)	Not reached (2.1+, 17.8+)	6.2 (1.4+, 8.8+)
% ongoing	73%	72%	34%
TPS ≥50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	14.9 (10.4, NA)	17.3 (11.8, NA)	8.2 (6.4, 10.7)
PFS‡			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)

Overall response rate‡			
ORR %§ (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
Response duration‡,¶,Þ			
Median in months (range)	Not reached (0.7+, 16.8+)	Not reached (2.1+, 17.8+)	8.1 (2.1+, 8.8+)
% ongoing	76%	75%	33%

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† Based on stratified Log rank test

‡ Assessed by BICR using RECIST 1.1

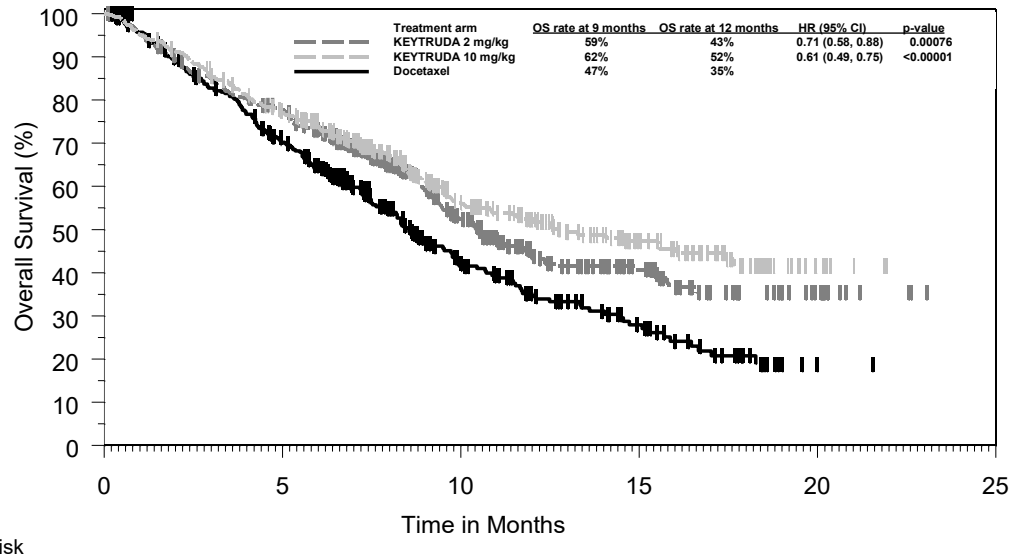
§ All responses were partial responses

¶ Based on patients with a best overall response as confirmed complete or partial response

Includes 30, 31, and 2 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

Þ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

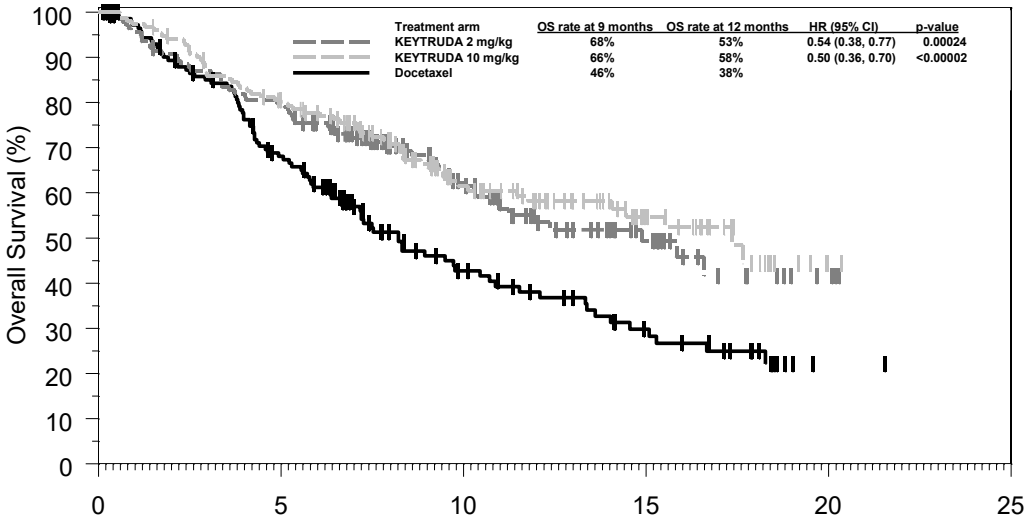
Figure 14: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



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

Figure 15: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk

KEYTRUDA 2 mg/kg:	139	110	51	20	3	0
KEYTRUDA 10 mg/kg:	151	115	60	25	1	0
Docetaxel:	152	90	38	19	1	0

Efficacy results were similar for the 2 mg/kg and 10 mg/kg KEYTRUDA arms. Efficacy results for OS were consistent regardless of the age of tumor specimen (new versus archival).

KEYNOTE-001: Open label study in NSCLC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was also investigated in a multicenter, open-label, randomized, dose-comparative cohort of KEYNOTE-001. Patients had advanced NSCLC that was PD-L1 positive, with progression of disease following treatment with platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations had disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. The trial 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. Patients were randomized to receive 10 mg/kg of KEYTRUDA every 2 (n=69) or 3 (n=87) weeks until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR (according to RECIST 1.1 as assessed by blinded independent central review) and duration of response.

The prevalence of patients with a PD-L1 expression TPS greater than or equal to 50% among screened patients with NSCLC as ascertained retrospectively by the companion diagnostic PD-L1 IHC 22C3 pharmDx™ kit was 26%. Among the randomized patients with tumor samples evaluable for PD-L1 expression, 61 had TPS greater than or equal to 50%. The baseline characteristics for this population included: median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous and non-squamous (21% and 75%, respectively); M1 (98%); brain metastases (11%); and one (25%), two (31%), or three or more (44%) prior therapies. The mutation status among patients was EGFR (10%), ALK (0%), or KRAS (16%).

Efficacy results for NSCLC patients treated with 10 mg/kg every 2 or 3 weeks in KEYNOTE-001 are summarized in Table 21.

Table 21: Response to KEYTRUDA 10 mg/kg every 2 or 3 Weeks in Previously Treated NSCLC Patients with PD-L1 expression TPS ≥50% (n=61)

Endpoint	
Best Overall Response*	
ORR %, (95% CI)	43% (30, 56)
Complete response	2%
Partial response	41%
Response Duration†	
Median in months (range)	Not reached (2.1+, 13.4+)
% ongoing	65%‡
Time to Response†	
Median in months (range)	2.1 (1.4, 6.2)
PFS§	
Median in months (95% CI)	6.3 (2.1, 10.7)
6-month PFS rate	53%
OS§	
12-month OS rate	60%

*Based on all patients treated (n=61), with assessment by independent review and RECIST 1.1

†Based on patients (n=26) with a confirmed response by independent review

‡Includes 17 patients with ongoing responses of 6 months or longer

§ Based on all treated patients (n=61)

Similar ORR results were observed in another group of patients (n=25) with TPS greater than or equal to 50% receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks in KEYNOTE-001.

KEYNOTE-091: Controlled trial for the adjuvant treatment of patients with resected NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-091, a multicenter, randomized, triple-blind, placebo-controlled trial. Key eligibility criteria were completely resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC by AJCC 7th edition, regardless of tumor PD-L1 expression status, no prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy, and no prior or planned adjuvant radiotherapy for the current malignancy. Patients may or may not have received adjuvant chemotherapy. 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. Randomization 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 randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately one year (18 doses). Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA 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 1177 patients randomized in KEYNOTE-091, 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; and 77% White, 18% Asian, 86% current or former smokers; and 39% had ECOG performance of

1. Eleven percent had stage IB (T2a ≥4 cm), 57% had stage II, and 31% had stage IIIA disease. Thirty-nine percent had tumor PD-L1 expression 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 primary efficacy outcome measures were investigator-assessed disease free survival (DFS) in the overall population and in the population with tumor PD-L1 expression TPS ≥50%, where DFS was defined as the time between the date of randomization 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 tumor PD-L1 expression TPS ≥1%, and OS in the overall population and in the populations with tumor PD-L1 expression TPS ≥50% and TPS ≥1%.

The trial demonstrated a statistically significant improvement in DFS in the overall population at a pre-specified interim analysis [HR = 0.76 (95% CI: 0.63, 0.91; p = 0.0014)] for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 576 patients with Stage II NSCLC who received adjuvant chemotherapy in KEYNOTE-091, the DFS HR was 0.64 (95% CI: 0.48, 0.84). OS results were not mature with only 42% of pre-specified OS events in the overall population. The median follow-up time was 32.4 months (range: 0.6 to 68 months). Efficacy results for patients who received adjuvant chemotherapy in KEYNOTE-091 are summarized in Table 22 and Figure 16.

Table 22: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

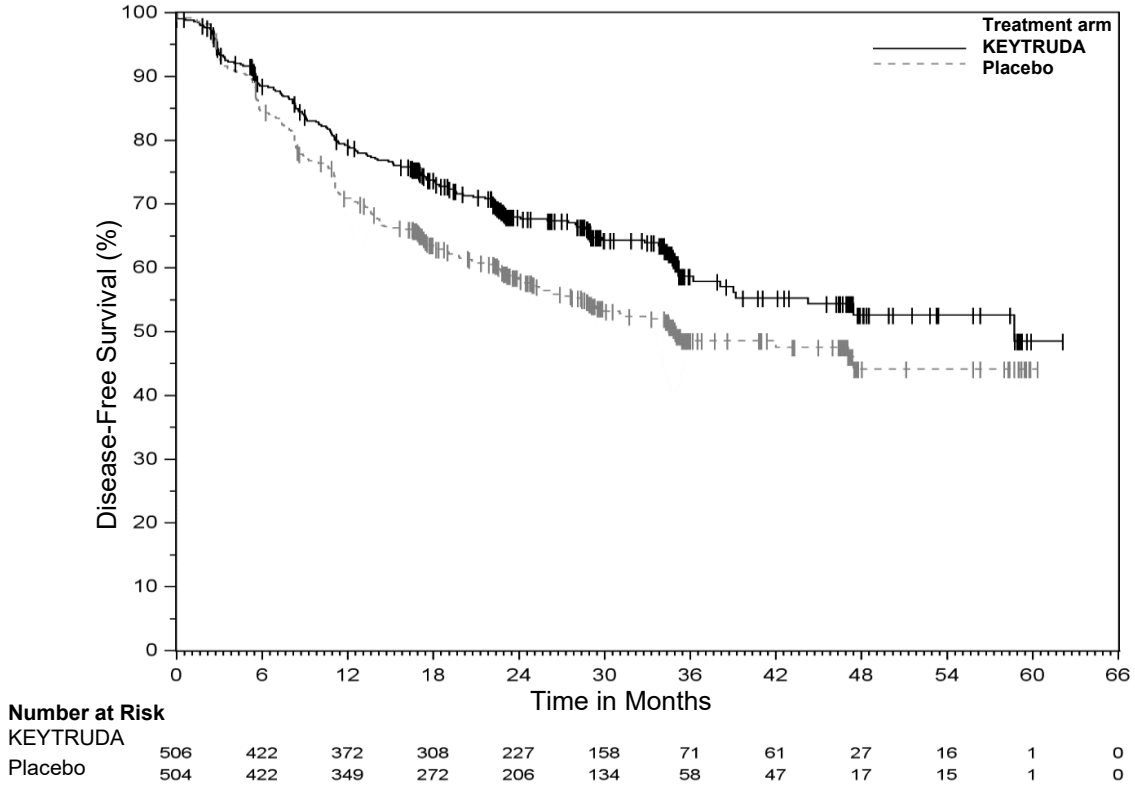
Endpoint	KEYTRUDA 200 mg every 3 weeks n=506	Placebo n=504
DFS		
Number (%) of patients with event	177 (35%)	231 (46%)
Hazard ratio* (95% CI)	0.73 (0.60, 0.89)	

Median in months (95% CI)	58.7 (39.2, NR)	34.9 (28.6, NR)

* Based on the unstratified univariate Cox regression model

NR = not reached

Figure 16: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy



KEYNOTE-671: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable NSCLC

The efficacy of KEYTRUDA in combination with platinum-containing chemotherapy given as neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in KEYNOTE-671, a multicenter, randomized, double-blind, placebo-controlled trial. Key eligibility criteria were previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition, regardless of tumor 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. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression

(TPS ≥50% or <50%), histology (squamous vs. non-squamous), 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. 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. 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 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 randomized: 397 patients to the KEYTRUDA 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 2.0% 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 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 had definitive surgery compared to 76% of patients in the 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 monotherapy compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone. OS efficacy results with a median follow-up time of 29.8 months (range: 0.4 to 62.0 months) are summarized in Table 23 and Figure 17. EFS, pCR, and mPR efficacy results with a median follow-up time of 21.4 months (range: 0.4 to 50.6 months) are summarized in Table 23.

Table 23: Efficacy Results in KEYNOTE-671

Endpoint	**KEYTRUDA 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‡	0.00517	
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	
pCR		
Number of patients with pCR	72	16
pCR Rate (%), (95% CI)	18.1 (14.5, 22.3)	4.0 (2.3, 6.4)
Treatment difference estimate (%), (95% CI)§	14.2 (10.1, 18.7)	
p-Value	< 0.0001	
mPR		

Number of patients with mPR	120	44
mPR Rate (%), (95% CI)	30.2 (25.7, 35.0)	11.0 (8.1, 14.5)
Treatment difference estimate (%), (95% CI)§	19.2 (13.9, 24.7)	
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

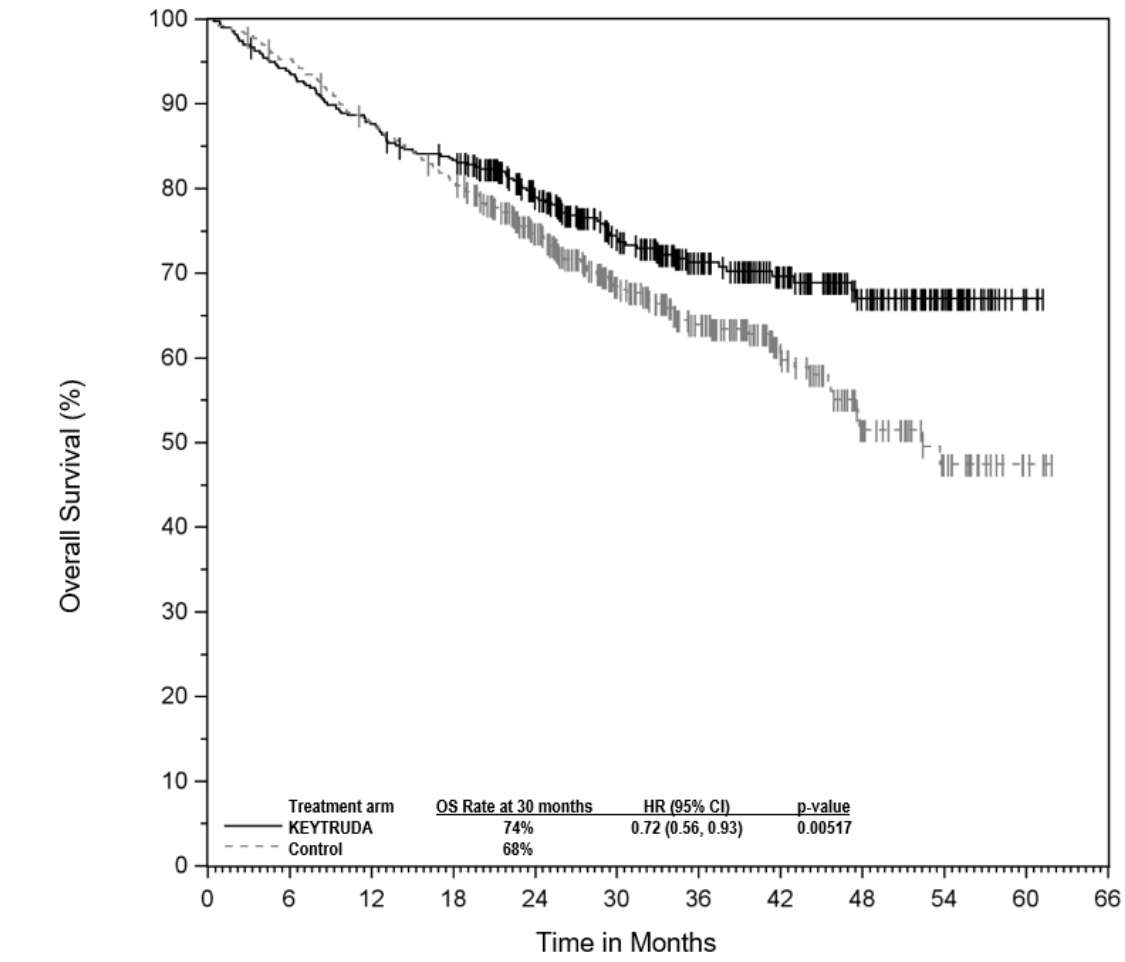
‡ Based on stratified log-rank test

§ Based on Miettinen and Nurminen method stratified by stage, tumor PD-L1 expression, histology, and geographic region

NR = not reached

The final EFS analysis was performed at a median duration of follow-up of 29.8 months after 422 patient events (174 for the KEYTRUDA arm and 248 for the placebo arm). Median EFS was 47.2 months (95% CI: 32.9, NR) for the KEYTRUDA arm and 18.3 months (95% CI: 14.8, 22.1) for the placebo arm. The EFS HR was 0.59 (95% CI: 0.48, 0.72). See Figure 18.

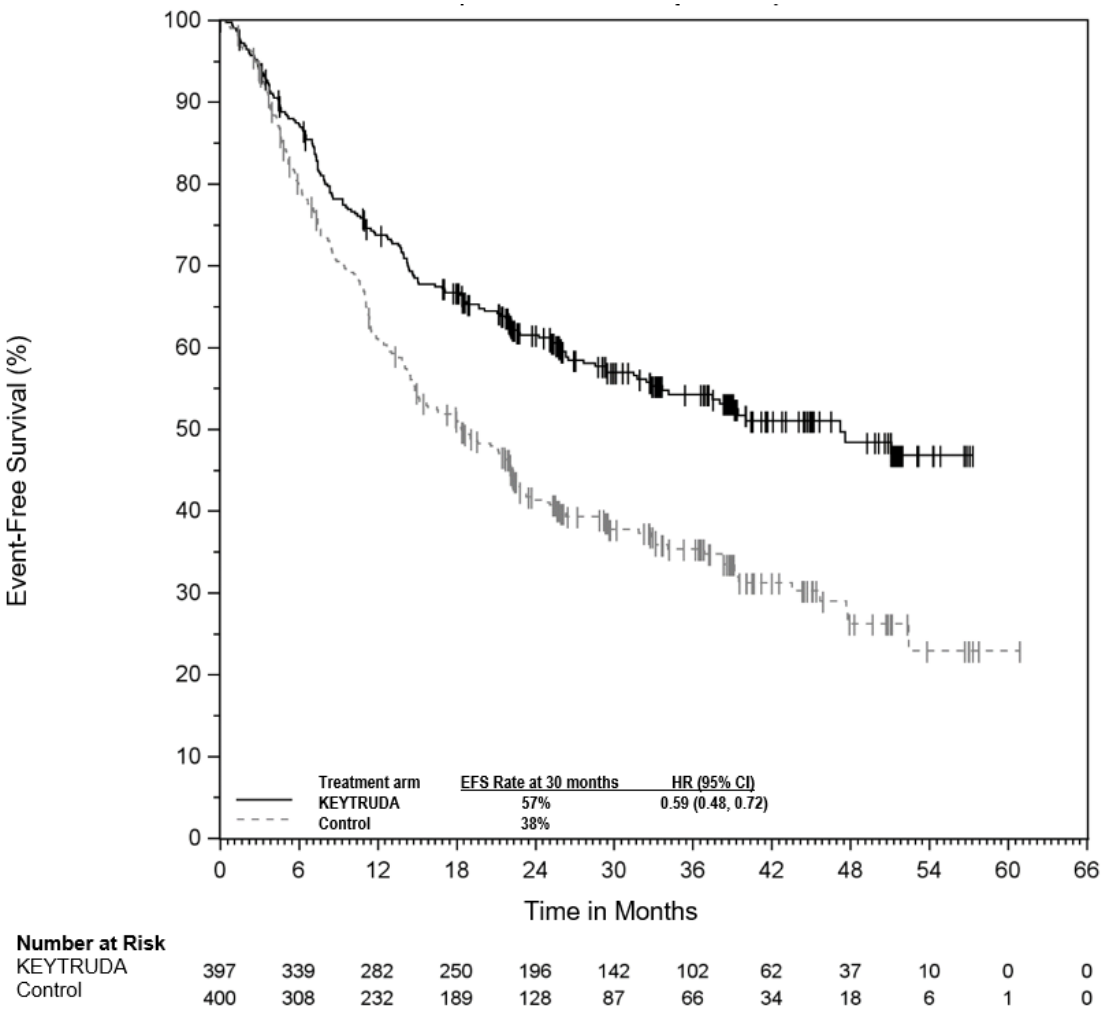
Figure 17: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



Number at Risk

KEYTRUDA	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 18: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



Malignant Pleural Mesothelioma

KEYNOTE-483: Controlled trial of combination therapy in patients with untreated unresectable advanced or metastatic MPM

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, open-label, active-controlled trial, KEYNOTE-483. Key eligibility criteria were unresectable advanced or metastatic MPM with no prior systemic therapy for advanced/metastatic disease. Patients were enrolled regardless of tumor PD-L1 expression. Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomized (1:1) to one of the

following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles.

Treatment with KEYTRUDA continued until disease progression as determined by the investigator according to modified RECIST 1.1 for mesothelioma (mRECIST), unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks for 18 weeks, followed by every 12 weeks thereafter.

Among the 440 patients in KEYNOTE-483 (222 patients in the KEYTRUDA combination arm and 218 in the chemotherapy arm), baseline characteristics were: median age of 70 years (77% age 65 or older); 76% male; 79% White, 21% not reported or unknown; 2% Hispanic or Latino; and 47% and 53% ECOG performance status of 0 or 1, respectively. Seventy-eight percent had epithelioid and 22% had non-epithelioid histology.

The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST, and health related quality of life as assessed using EORTC QLQ-C30 and EORTC QLQ-LC13. The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to KEYTRUDA in combination with chemotherapy compared with patients randomized to chemotherapy alone. The median follow-up time was 17 months (range: 0.8 – 60.3 months). Table 24 and Figures 19 and 20 summarize key efficacy measures for KEYNOTE-483.

Table 24: Efficacy Results in KEYNOTE-483

Endpoint	KEYTRUDA 200 mg every 3 weeks + Pemetrexed + Platinum Chemotherapy (n=222)	Pemetrexed + Platinum Chemotherapy (n=218)
OS*		
Number (%) of patients with event	167 (75%)	175 (80%)
Hazard ratio† (95% CI)	0.79 (0.64, 0.98)	
p-Value‡	0.0162	
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
PFS*,§		
Number (%) of patients with event	190 (86%)	166 (76%)
Hazard ratio† (95% CI)	0.80 (0.65, 0.99)	
p-Value‡	0.0194	
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Objective Response Rate§,¶		
ORR % (95% CI)	52% (45.5, 59.0)	29% (23.0, 35.4)
Number (%) of complete responses	1 (0.5%)	0 (0%)
Number (%) of partial responses	115 (52%)	63 (29%)
p-Value#	<0.00001	
Response Duration*,§,Þ		
Median in months (range)	6.9 (1.2+, 38.9+)	6.8 (1.4+, 25.1+)
% with duration ≥12 monthsβ	23%	13%

* Based on the final analysis

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by histological subtype at randomization (epithelioid vs. other subtypes).

‡ Based on stratified log-rank test

§ Assessed by BICR using mRECIST

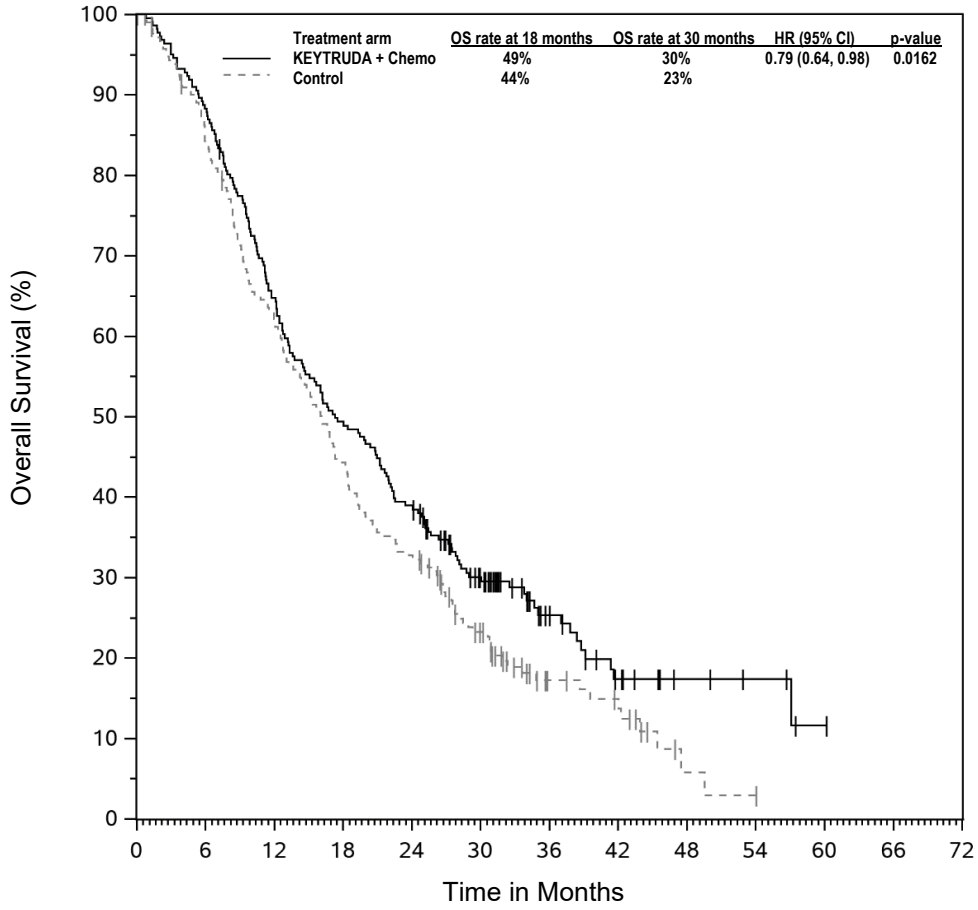
¶ Based on an interim analysis

Based on Miettinen and Nurminen method stratified by histological subtype at randomization (epithelioid vs other subtypes).

Þ Based on patients with a best overall response as confirmed complete or partial response; n=117 for patients in the KEYTRUDA combination arm; n=64 for patients in the chemotherapy arm

β Based on Kaplan-Meier estimates

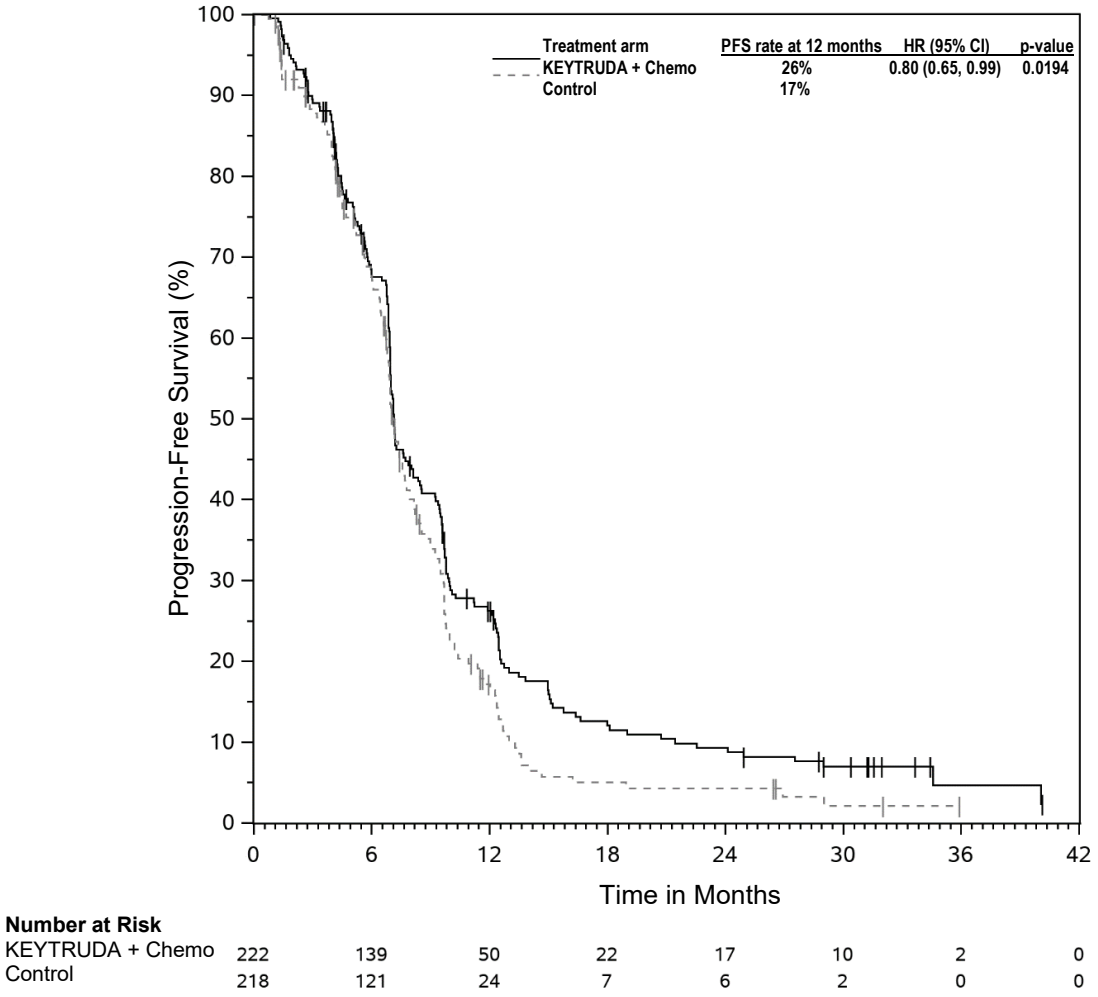
Figure 19: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483



Number at Risk

KEYTRUDA + Chemo	222	196	143	109	86	54	25	13	6	4	1	0	0
Control	218	176	128	92	68	40	16	12	2	1	0	0	0

Figure 20: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-483



Health-related QoL as evaluated by the EORTC QLQ-C30 (GHS/QoL, physical functioning, and dyspnea) and EORTC QLQ-LC13 (chest pain and cough) was generally maintained in patients receiving KEYTRUDA in combination with chemotherapy as compared to chemotherapy alone.

Head and Neck Cancer

KEYNOTE-689: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable locally advanced HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE 689, a randomized, multicenter, open-label, active controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC. 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 primary

tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS<50%) according to the PD-L1 IHC 22C3 pharmDx kit.

Patients were randomized (1:1) to one of the following treatment arms:

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, KEYTRUDA 200 mg for 3 cycles in combination with either radiation + 3 cycles of cisplatin 100 mg/m^2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.
- Treatment Arm B: no neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, either radiation + 3 cycles of cisplatin 100 mg/m^2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery.

Treatment with KEYTRUDA continued until RECIST v1.1 defined progression of disease as assessed by BICR, 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 prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed 12 weeks after end of RT ± cisplatin treatment and then every 3 months until the end of Year 3; then every 6 months thereafter up to the end of Year 5. In Arm A, 89% of patients had surgery, compared to 88% in Arm B. In Arm A, 29% of patients received cisplatin plus radiation and 46% received radiation alone. In Arm B, 40% of patients received cisplatin plus radiation, and 39% received radiation alone.

The main efficacy outcome measure was event-free survival (EFS) by BICR 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 disease progression or recurrence, or death due to any cause. Secondary primary malignancy was not considered an event. Additional efficacy outcome measures were major

pathological response (mPR) as assessed by BIPR, overall survival (OS), and pathological complete response (pCR) as assessed by BIPR.

The study population characteristics in the 682 patients with PD-L1 expression of CPS ≥1 were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black, 14% were Hispanic or Latino; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumors were HPV positive, and 26% had Stage III disease, 74% had Stage IVA disease. Ninety-six percent of patients' tumors had PD-L1 expression of CPS ≥1 and 65% had CPS ≥10.

The trial demonstrated a statistically significant improvement in EFS for patients randomized to KEYTRUDA in combination with radiation with or without cisplatin compared to those randomized to radiation with or without cisplatin at the first pre-specified interim analysis. Table 25 and Figures 21 and 22 describe efficacy results for the pre-specified subgroup of patients whose tumours expressed PD-L1 with CPS ≥ 1 at a median follow-up time of 27.0 months (range: 0.5 to 66.5 months) in KEYNOTE-689.

Table 25: Efficacy Results for Perioperative KEYTRUDA with adjuvant RT with or without cisplatin in Patients with HNSCC CPS≥1 in KEYNOTE-689

Endpoint	KEYTRUDA 200 mg every 3 weeks with RT with or without cisplatin n=363	RT with or without cisplatin n=351
EFS		
Number of patients with event (%)	128 (37%)	156 (47%)
Median in months* (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
Hazard ratio† (95% CI)	0.70 (0.55, 0.89)	
p-Value‡,	0.00140	
mPR		
Number of patients with mPR	34	0
mPR Rate (%), (95% CI)	9.8 (6.9, 13.4)	0.0 (0.0, 1.1)
mPR Rate difference estimate (%), (95% CI)§	9.8 (7.0, 13.3)	
p-Value‖	<0.00001	

* From product-limit (Kaplan-Meier) method for censored data.

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site and tumor stage.

‡ One-sided p-value based on log-rank test stratified by primary tumor site and tumor stage. Compared to a one-sided p-value boundary of 0.0124.

§ Based on Miettinen and Nurminen method stratified by primary tumor site and tumor stage.

‖ Compared to a one-sided p-value boundary of 0.0005

NR = not reached

Figure 21: Kaplan-Meier Curve for Event-free Survival for KEYTRUDA in Patients with HNSCC CPS≥1 in KEYNOTE-689

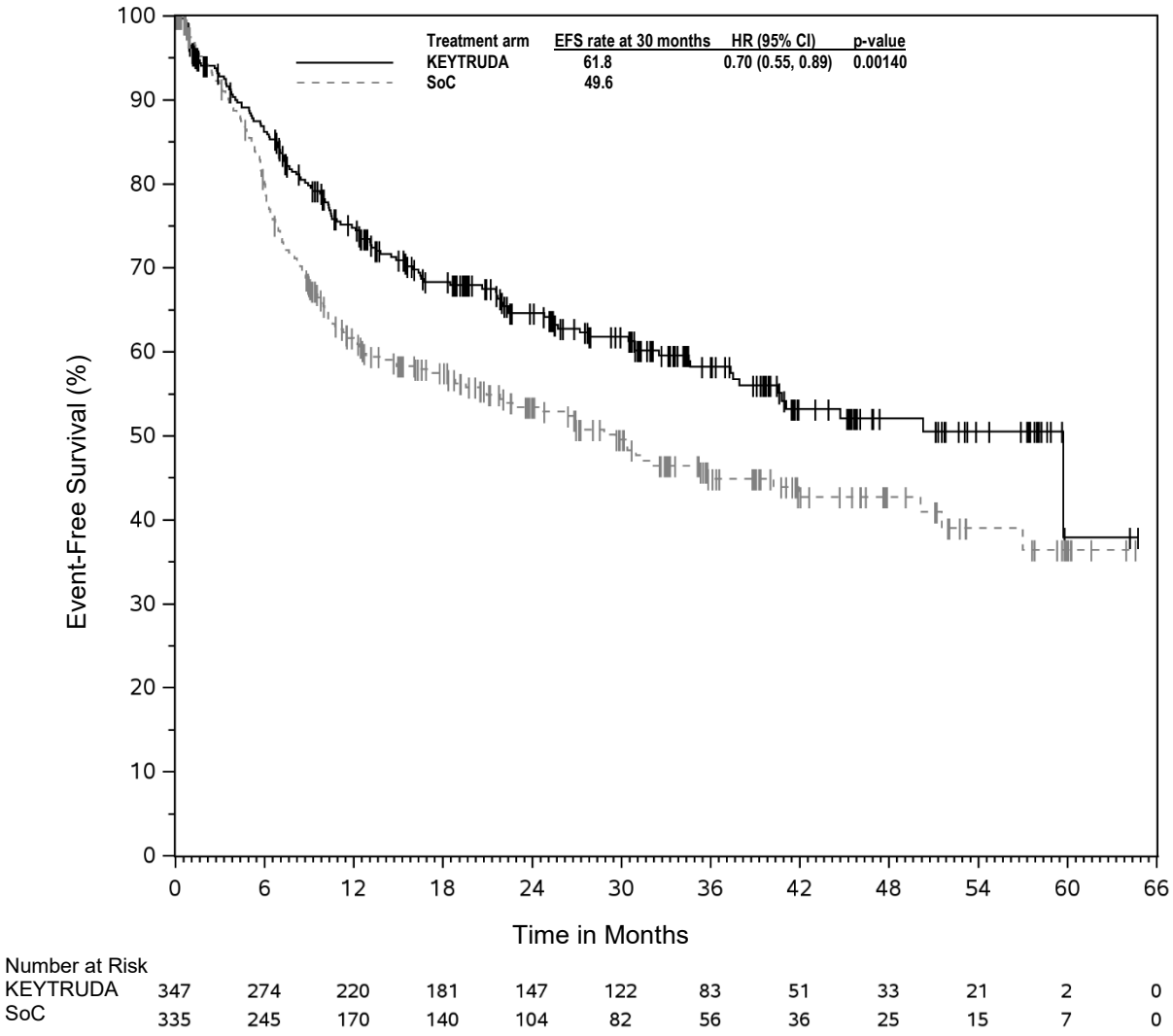
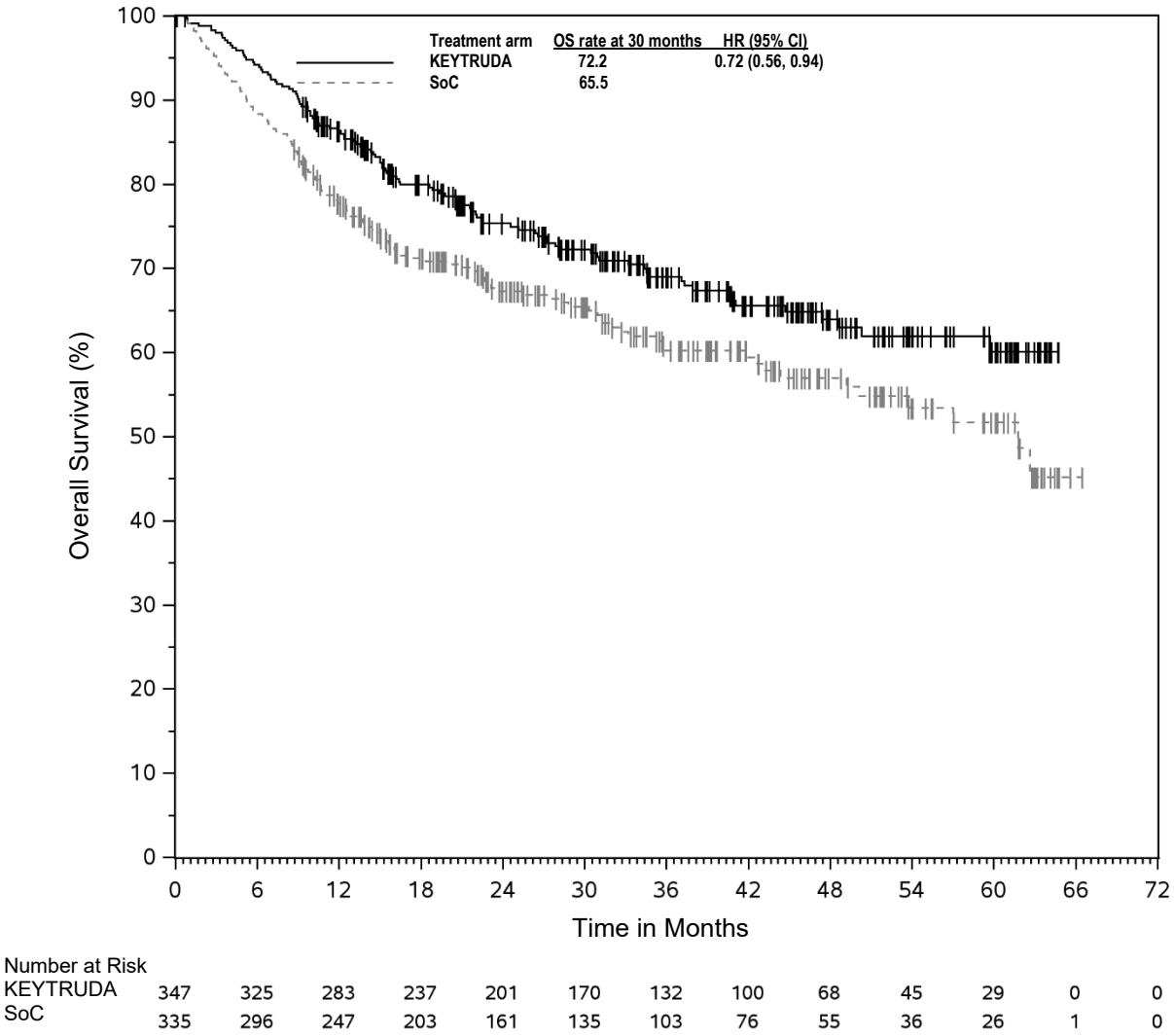


Figure 22: Kaplan-Meier Curve for Overall Survival for KEYTRUDA in Patients with HNSCC CPS≥1 KEYNOTE-689



At the time of the pre-specified interim analysis of OS with 76% of OS events, HR estimate (HR: 0.72; 95%CI: 0.56, 0.94) favored KEYTRUDA in combination with radiation with or without cisplatin compared to radiation with or without cisplatin in the CPS ≥1 population. The pCR rates were 3.2% in patients randomized to KEYTRUDA in combination with radiation with or without cisplatin and 0% in radiation with or without cisplatin in the CPS ≥1 population.

KEYNOTE-048: Controlled trial of first-line monotherapy or combination therapy in HNSCC

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-048, a multicenter, randomized, open-label, active-controlled study in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and 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 for the study. Randomization was stratified by tumor PD-L1 expression (TPS≥50% or <50%) based on the PD-L1 IHC 22C3 pharmDx™ kit, HPV status (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 every 3 weeks
- KEYTRUDA 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 1000 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 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)

Treatment with KEYTRUDA continued until RECIST 1.1-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 total of 882 patients were randomized; 301 patients to the KEYTRUDA monotherapy arm, 281 patients to the KEYTRUDA plus chemotherapy arm, and 300 patients to the standard treatment arm. The study population characteristics were: median age of 61 years (range: 20 to 94); 36% age 65 or older; 83% male; 73% White and 20% Asian; 61% ECOG PS of 1; and 79% were former/current smokers. Disease characteristics were: 22% HPV positive, 85%, 43%, and 23% had PD-L1 expression defined as CPS ≥1,

CPS ≥20, and TPS ≥50%, respectively, and 95% had Stage IV disease (Stage IVa 19%, Stage IVb 6%, and Stage IVc 70%).

The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). ORR, as assessed by BICR according to RECIST 1.1, was a secondary outcome measure. The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to standard treatment. OS for patients randomized to KEYTRUDA monotherapy was non-inferior compared to standard treatment. Tables 26 and 27 and Figures 23 and 24 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

Table 26: Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥1)

Endpoint	**KEYTRUDA Platinum Chemotherapy 5-FU n=242**	**Standard Treatment* n=235**
OS		
Number (%) of patients with event	164 (68%)	190 (81%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.7 (9.3, 11.7)
Hazard ratio† (95% CI)	0.71 (0.57, 0.88)	
p-Value‡	0.0007	
PFS		
Number of patients with event (%)	206 (85%)	215 (92%)
Median in months (95% CI)	5.0 (4.7, 6.2)	5.0 (4.8, 5.8)
Hazard ratio† (95% CI)	0.82 (0.67, 1.00)	
p-Value‡	0.0228	
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+, 30.4+)	4.3 (1.2+, 27.9+)
% with duration ≥6 months	54%	34%

Results at a pre-specified interim analysis

* Cetuximab, platinum, and 5-FU

† Based on the stratified Cox proportional hazard model

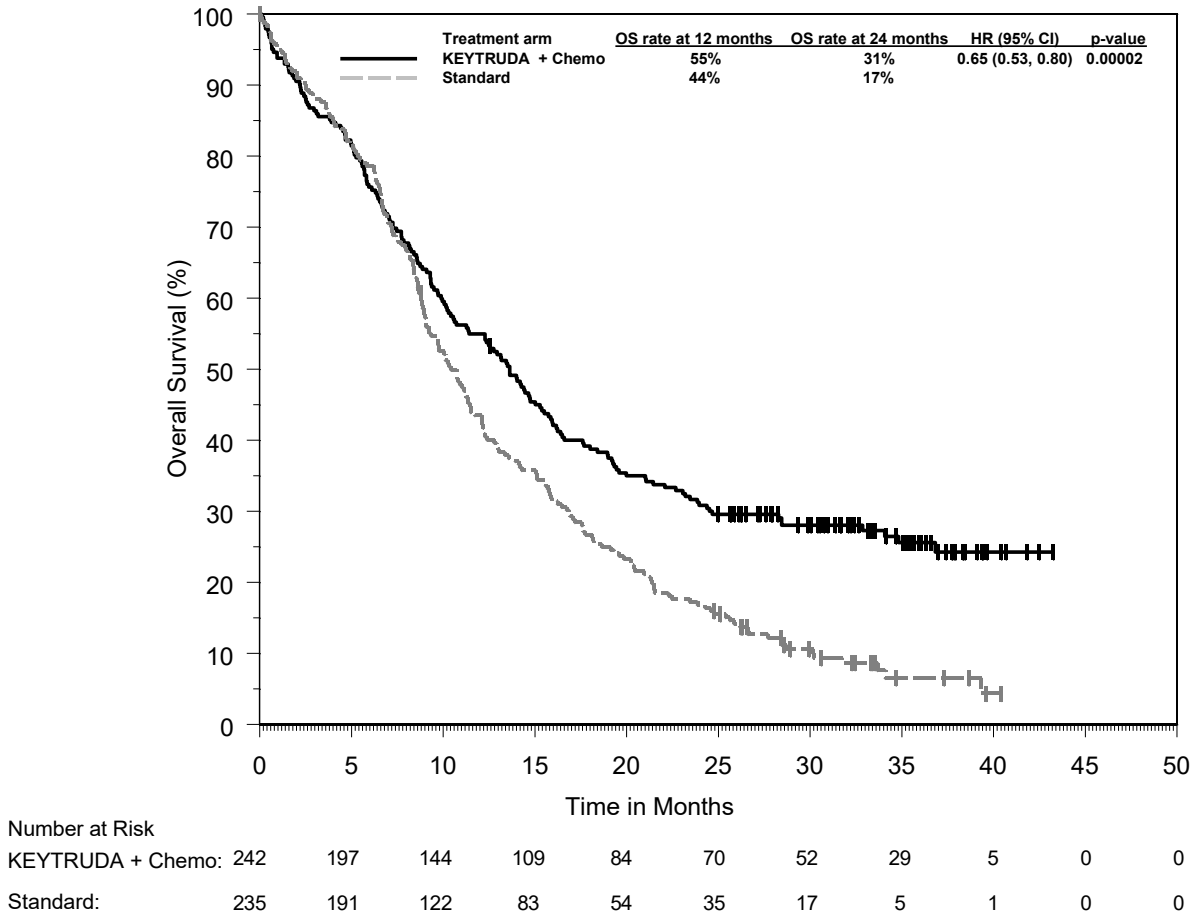
‡ Based on stratified log-rank test

§ 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)

In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI: 0.51, 0.94). The OS HRs at final analysis with a median follow-up of 11.4 months were similar to those obtained at the pre-specified interim analysis and in addition, demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 and CPS ≥20: ITT (0.72, 95% CI: 0.60, 0.87), CPS ≥1 (0.65, 95% CI: 0.53, 0.80), CPS ≥20 (0.60, 95% CI: 0.45, 0.82).

Figure 23: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥1)*



*Median follow-up of 11.5 months at protocol-specified final analysis

Table 27: Efficacy Results for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS ≥1)

Endpoint	KEYTRUDA n=257	Standard Treatment* n=255
OS		
Number (%) of patients with event	177(69%)	206 (81%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)
Hazard ratio† (95% CI)	0.78 (0.64, 0.96)	
p-Value‡	0.0085	
PFS		

Number of patients with event (%)	225 (88%)	231 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)
Hazard ratio† (95% CI)	1.16 (0.96, 1.39)	
p-Value‡	0.9330	
Objective Response Rate		
ORR§ (95% CI)	19% (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)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)
% with duration ≥6 months	79%	36%

Results at a pre-specified interim analysis

* Cetuximab, platinum, and 5-FU

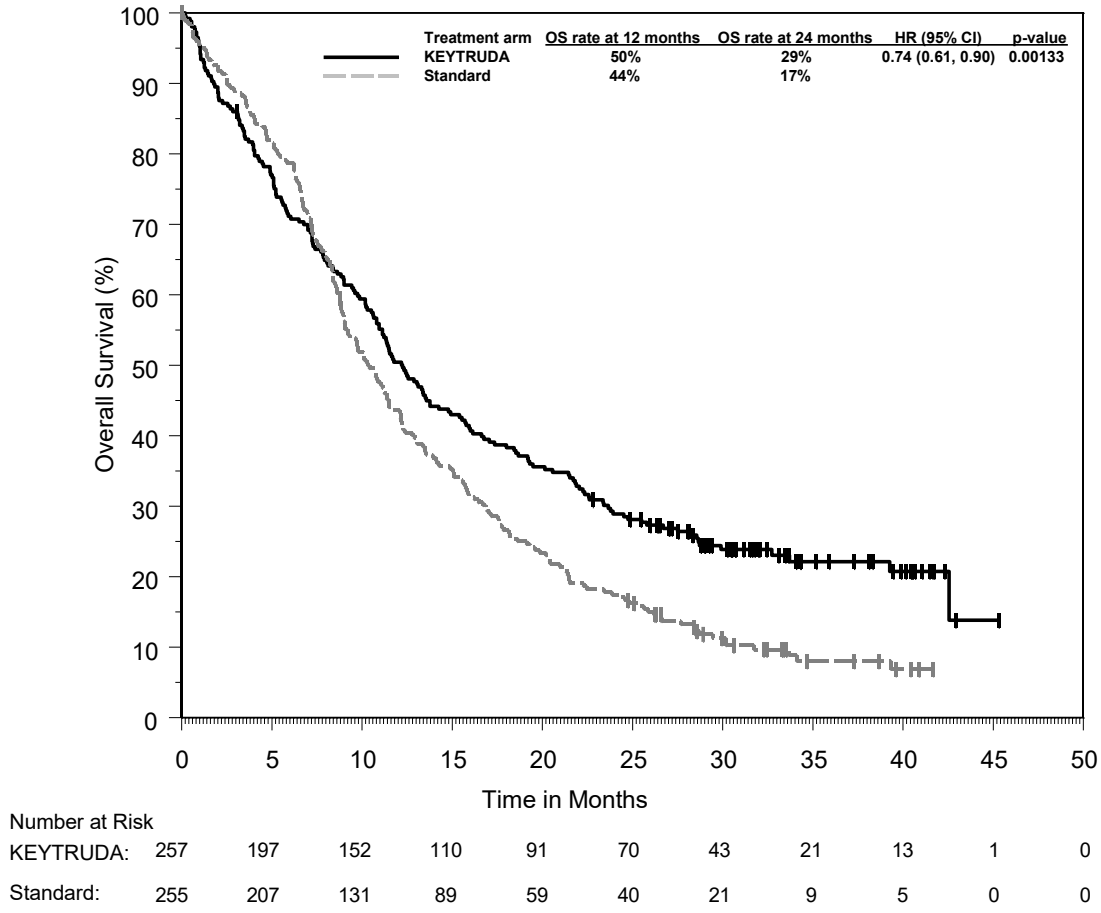
† Based on the stratified Cox proportional hazard model

‡ 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 KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS≥1)*



*Median follow-up of 11.4 months at protocol-specified final analysis.

Additional OS analyses based on PD-L1 expression (CPS ≥1 and CPS ≥20) were performed in KEYNOTE-048. The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA monotherapy compared to standard treatment for PD-L1 expression CPS ≥1 and CPS ≥20. OS for patients who had PD-L1 CPS ≥1 or CPS ≥20 for KEYTRUDA monotherapy compared to standard treatment is summarized in Table 28.

Table 28: OS by PD-L1 Expression

	CPS ≥1		CPS ≥20	
	KEYTRUDA n=257	Standard Treatment* n=255	KEYTRUDA n=133	Standard Treatment* n=122
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‡	0.0085		0.0007	

Results at a pre-specified interim analysis

* Cetuximab, platinum, and 5-FU

† Hazard ratio (compared to standard treatment) based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test

The final OS analysis was performed for patients with CPS ≥1 with a median follow-up of 11.4 months from the pre-specified interim analysis. Median OS was 12.3 months (95% CI: 10.8, 14.3) for KEYTRUDA as a single agent and 10.3 months (95% CI: 9.0, 11.5) for cetuximab in combination with chemotherapy, with an HR of 0.74 (95% CI: 0.61, 0.90).

The final OS analysis was performed for patients with CPS ≥20 with a median follow-up of 12.2 months from the pre-specified interim analysis. Median OS was 14.8 months (95% CI: 11.5, 20.6) for KEYTRUDA as a single agent and 10.7 months (95% CI: 8.8, 12.8) for cetuximab in combination with chemotherapy, with an HR of 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, 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 0.90 (95% CI: 0.68, 1.18). The final OS analysis was performed for patients with CPS 1-19 with a median follow-up of 10.3 months. At the final 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).

Esophageal Cancer

KEYNOTE-590: First-line treatment of locally advanced unresectable or metastatic Esophageal Cancer/Gastroesophageal Junction

The efficacy of KEYTRUDA was investigated in KEYNOTE-590, a multicenter, randomized, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction. 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 active autoimmune disease, a medical condition that required immunosuppression, or known HER-2 positive GEJ adenocarcinoma patients 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 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, 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 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, for up to 24 months.

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-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.

Among the 749 patients in KEYNOTE-590, 383 (51%) had tumours that expressed PD-L1 with a CPS ≥ 10. 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 KEYTRUDA 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 29 summarizes 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 25 and 26.

Table 29: Efficacy Results for KEYTRUDA plus chemotherapy in KEYNOTE-590 with PD-L1 expression (CPS ≥10)

Endpoint	**KEYTRUDA 200 mg every 3 weeks** **Cisplatin 5-FU n=186**	**Placebo** **Cisplatin 5-FU 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 (stratified log-rank)	<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 (stratified log-rank)	<0.0001	
Objective Response Rate‡		
ORR (stratified log-rank) % (95% CI)	51.1% (43.7, 58.5)	26.9% (20.8,33.7)
Complete response rate	5.9%	2.5%
Partial response rate	45.2%	24.4%
p-Value#	<0.0001	
Response Duration‡,§		
Median duration of response in months (range)	10.4 (1.9, 28.9+)	5.6 (1.5+, 25.0+)
% of patients with duration ≥6 months*	80.2%	47.7%
% of patients with duration ≥12 months*	43.7%	23.2%
% of patients with duration ≥18 months*	33.4%	10.4%

* Based on Kaplan-Meier estimation

† Based on the stratified Cox proportional hazard model

‡ Assessed by investigator using RECIST 1.1

One-sided p-Value for testing. H0: difference in % = 0 versus H1: difference in % > 0

§ Best objective response as confirmed complete response or partial response

Figure 25: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥10)

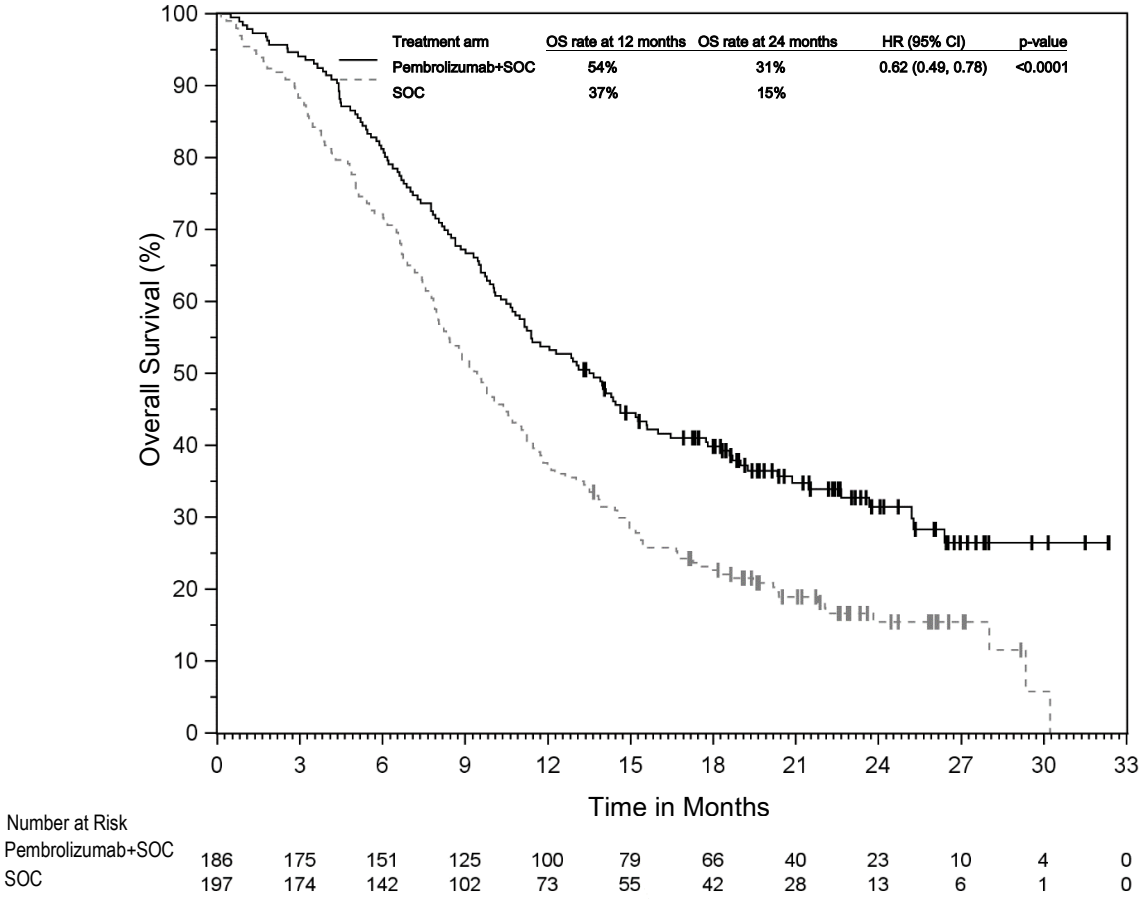
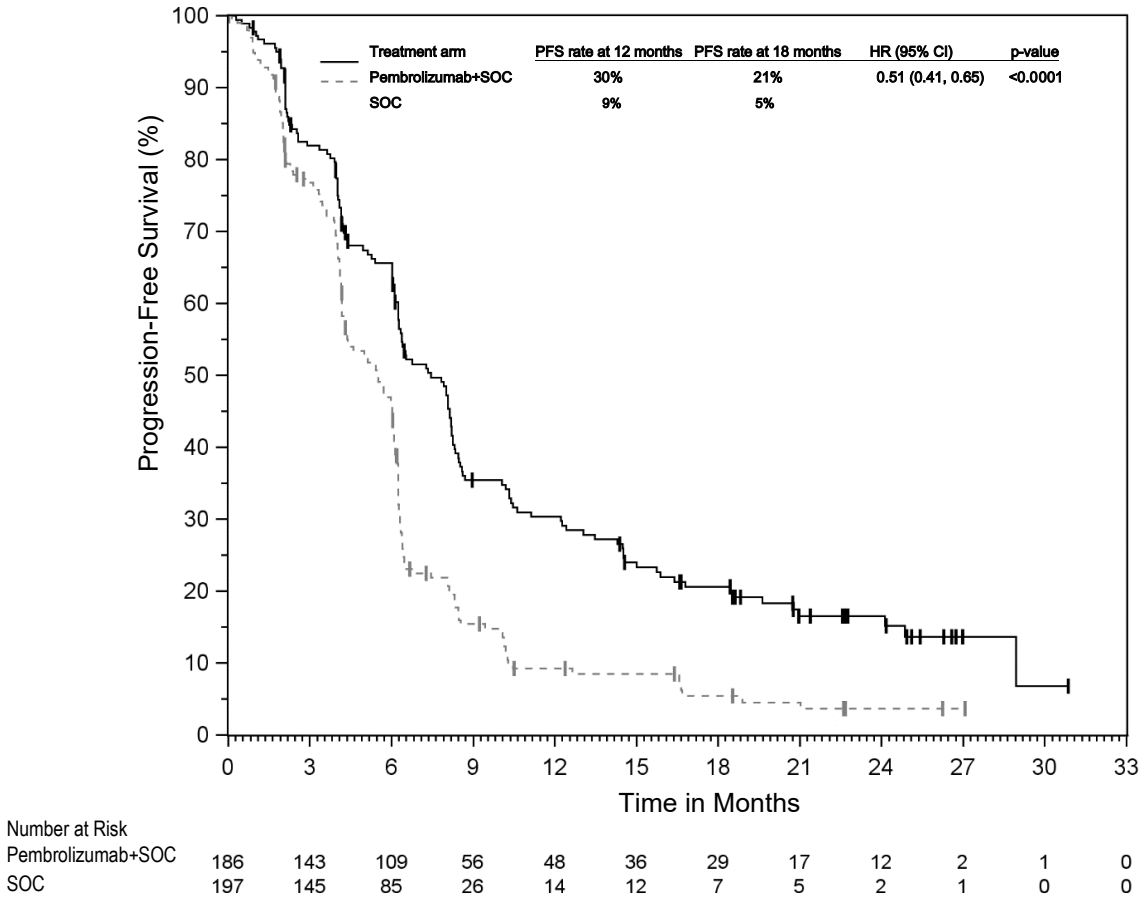


Figure 26: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥10)



Previously treated recurrent locally advanced or metastatic Esophageal Cancer

KEYNOTE-181: Controlled trial in esophageal cancer patients previously treated with systemic therapy

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-181, a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with esophageal cancer who progressed on or after prior systemic treatment for advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (N=314) or investigator's choice of any of the following chemotherapy regimens given

intravenously: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4 week cycle (n=145), docetaxel 75 mg/m^2 every 3 weeks (n=78), or irinotecan 180 mg/m^2 every 2 weeks (n=73). Treatment continued 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. 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 9 weeks. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and duration of response according to RECIST 1.1, as assessed by blinded independent central review.

Among the 628 patients, 35.4% (n=222) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 222 patients were: median age of 64 years (range: 33 to 81), 48% age 65 or older; 86% male; 45% White; 52% Asian; 36% had an ECOG PS of 0 and 64% had an ECOG PS of 1; 75% had squamous cell and 25% had adenocarcinoma histology; and 1% had a history of brain metastases. Ninety-one percent had M1 disease and 9% had M0 disease.

The trial demonstrated a statistically significant improvement in OS for patients whose tumors express PD-L1 with CPS ≥10 randomized to KEYTRUDA monotherapy as compared with chemotherapy. Table 30 summarizes the key efficacy measures for the CPS ≥10 population. The Kaplan-Meier curves for OS and PFS for the CPS ≥10 population are shown in Figures 27 and 28.

Table 30: Efficacy Results in Patients with Esophageal Cancer with PD-L1 expression CPS ≥10

Endpoint	KEYTRUDA 200 mg every 3 weeks n=107	Chemotherapy n=115
OS		
Number (%) of patients with event	87 (81%)	103 (90%)

Median in months (95% CI)	9.3 (6.6, 12.5)	6.7 (5.1, 8.2)
Hazard ratio* (95% CI)	0.69 (0.52, 0.93)	
p-Value (stratified log-rank)	0.0074	
PFS‡		
Number (%) of patients with event	96 (90%)	107 (93%)
Median in months (95% CI)	2.6 (2.1, 4.1)	3.0 (2.1, 3.7)
Hazard ratio* (95% CI)	0.73 (0.54, 0.97)	
p-Value (stratified log-rank)	0.015	
Objective Response Rate‡		
ORR % (95% CI)	22% (14, 31)	6% (3, 12)
Complete response rate	4%	1%
Partial response rate	18%	5%
p-Value (Miettinen-Nurminen)	0.0006	
Response Duration‡§		
Median duration of response in months (range)	9.3 (2.1+, 22.6+)	7.7 (4.3, 16.8+)
% of patients with duration ≥6 months†	77%	57%

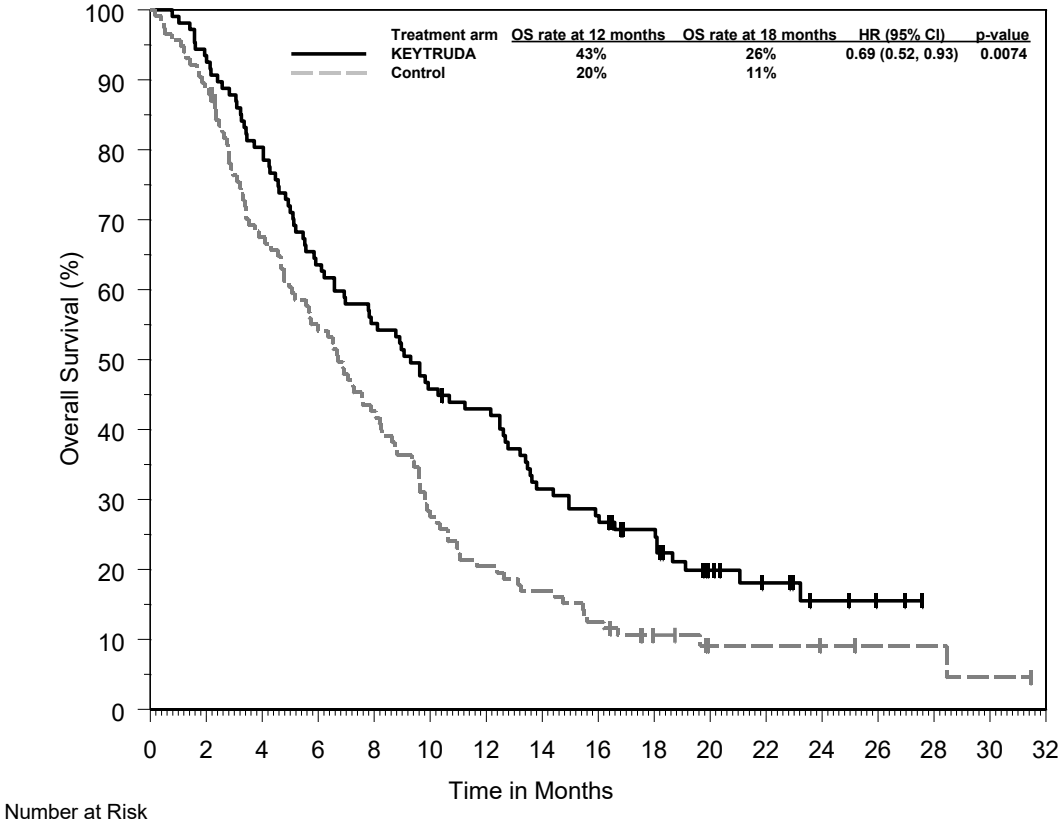
* Based on the stratified Cox proportional hazard model

† Based on Kaplan-Meier estimation

‡ Assessed by BICR using RECIST 1.1

§ Based on patients with a best overall response as confirmed complete or partial response

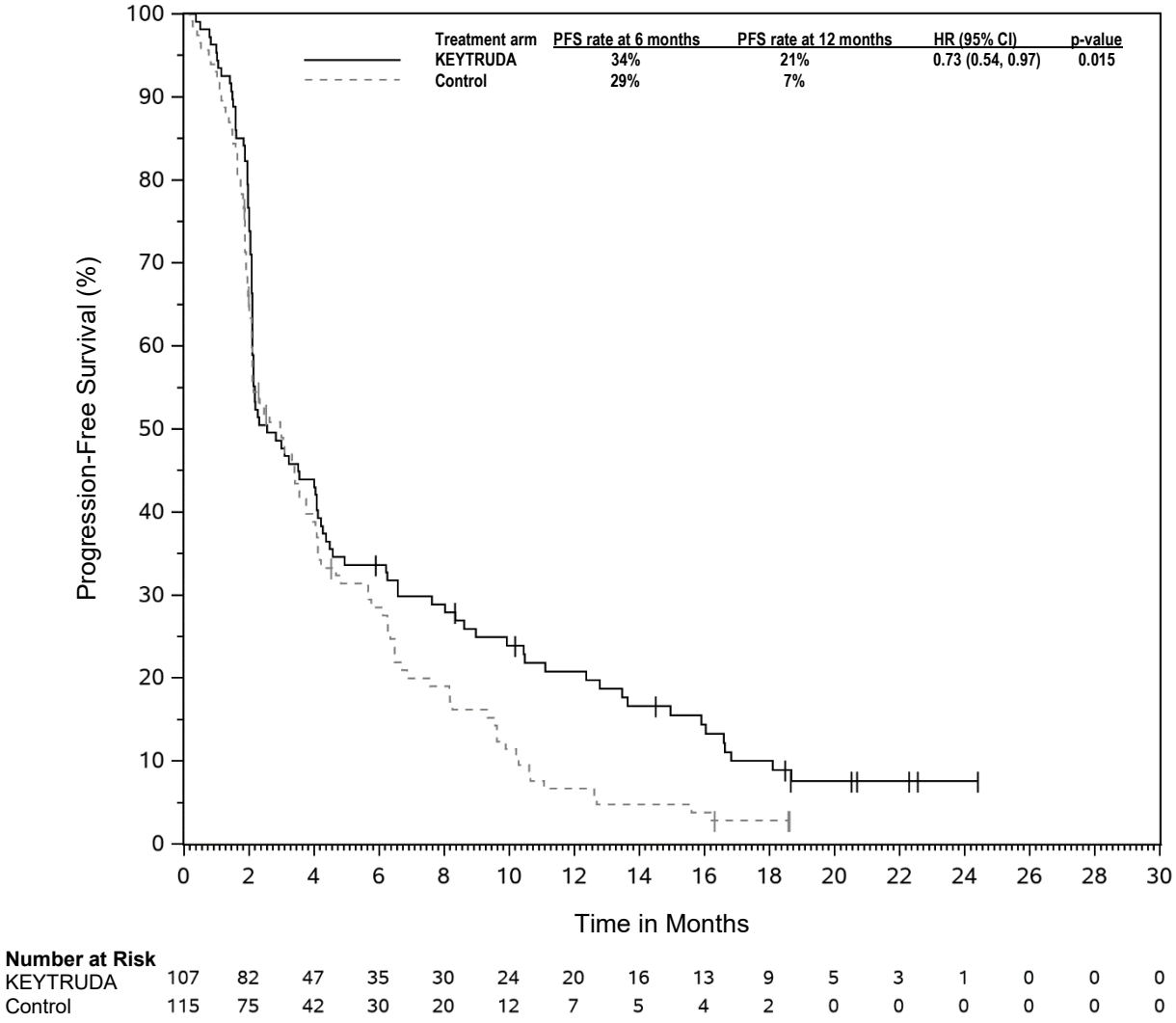
Figure 27: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-181 (CPS ≥10)



Number at Risk

KEYTRUDA:	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0	0
Control:	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1	0

Figure 28: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-181 (CPS ≥10)



KEYNOTE-045: Controlled trial in urothelial carcinoma patients previously treated with platinum-containing chemotherapy

The efficacy of KEYTRUDA was evaluated in KEYNOTE-045, a multicenter, randomized (1:1), active-controlled trial in 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=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Patients received KEYTRUDA 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. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. 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. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 57% ECOG performance status of 1 or greater; 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 as the most recent line of therapy. 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.

At a pre-specified interim analysis, the median follow-up time for 270 patients treated with KEYTRUDA was 10.3 months. The study demonstrated statistically significant improvements in OS and ORR for patients randomized to KEYTRUDA as compared to chemotherapy (Table 31 and Figure 29). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarized in Table 31.

Table 31: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy

Endpoint	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	155 (57%)	179 (66%)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value†	0.002	
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
PFS‡		
Number (%) of patients with event	218 (81%)	219 (81%)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value†	0.416	
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Objective Response Rate‡		
ORR % (95% CI)	21% (16, 27)	11% (8, 16)
Complete Response	7%	3%
Partial Response	14%	8%
p-Value§,	0.001	
Response duration‡,¶		
Median in months (range)	Not reached (1.6+, 15.6+)	4.3 (1.4+, 15.4+)
Number (%#) of patients with duration ≥6 months	41 (78%)	7 (40%)
Number (%#) of patients with duration ≥12 months	14 (68%)	3 (35%)

* Hazard ratio (KEYTRUDA 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

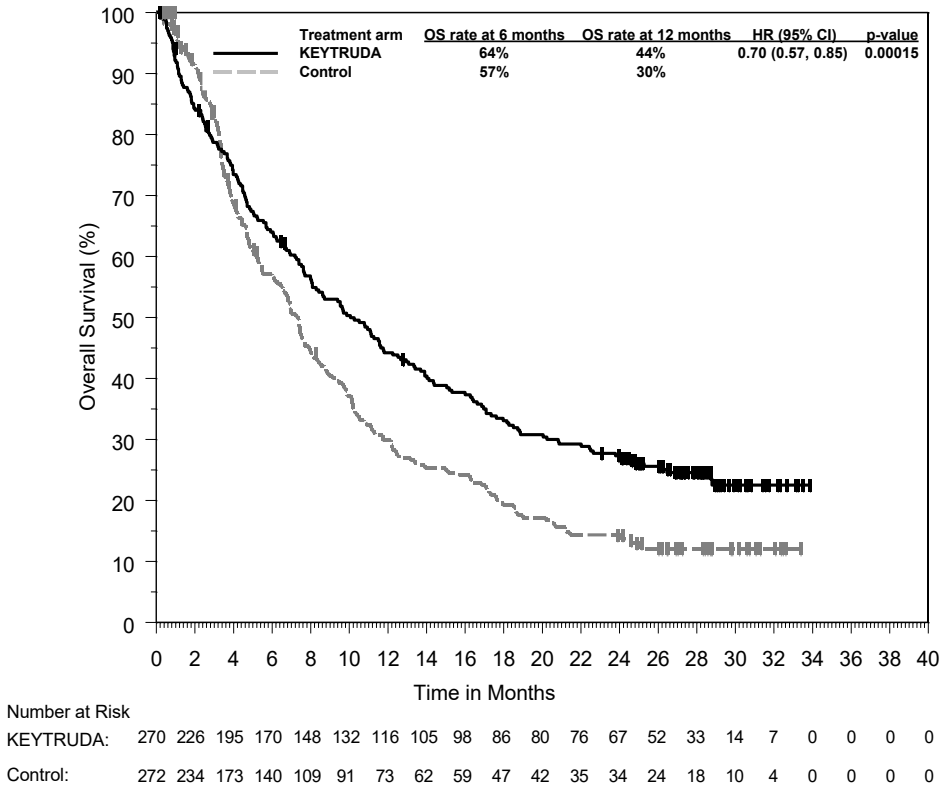
¶ Based on patients with a best overall response as confirmed complete or partial response

Based on Kaplan-Meier estimation

The final OS analysis was performed 13.6 months after the interim analysis with 419 patient events (200 for KEYTRUDA and 219 for chemotherapy). Median OS was 10.1 months (95% CI: 8.0, 12.3) for KEYTRUDA and 7.3 months (95% CI: 6.1, 8.1) for chemotherapy. The OS HR was 0.70 (95% CI: 0.57, 0.85; p<0.001). See Figure 29. In the final analysis there was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS.

At the final analysis, among the 57 responding patients who received KEYTRUDA vs. 30 responding patients who received chemotherapy, the median response duration was not reached (range 1.6+ to 30.0+ months) in patients who received KEYTRUDA, vs. 4.4 months (range 1.4+ to 29.9+ months) in patients who received chemotherapy. In patients who received KEYTRUDA, 84% had responses of 6 months or longer and 68% had responses of 12 months or longer (based on Kaplan-Meier estimation) vs. 47% who had responses of 6 months or longer and 35% who had responses of 12 months or longer (based on Kaplan-Meier estimation) in patients who received chemotherapy. The complete and partial response rates were 9% and 12%, respectively in patients who received KEYTRUDA vs. 3% and 8%, respectively in patients who received chemotherapy.

Figure 29: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population)



Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30. A prolonged time to deterioration in the EORTC QLQ-C30 global health status/QoL score 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 scores, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL scores. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Gastric Cancer

KEYNOTE-859: Controlled trial of combination therapy in HER2-negative gastric cancer patients naïve to treatment

The efficacy of KEYTRUDA in combination with fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-859, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or gastroesophageal junction (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. Randomization 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 randomized (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 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) for up to 35 cycles. KEYTRUDA 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 1000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. Placebo was administered prior to chemotherapy on Day 1 of each cycle.

Treatment with KEYTRUDA 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. Treatment was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumor status was performed every 6 weeks. The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DOR as assessed by BICR using RECIST v1.1.

The population characteristics were: median age of 62 years (range: 21 to 86), 39% age 65 or older; 68% male; 55% White and 34% Asian; 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) of patients 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. Efficacy results are summarized in Table 32.

Table 32: Efficacy Results for KEYNOTE-859

Endpoint	**KEYTRUDA 200 mg every 3 weeks FP or CAPOX n=790**	**Placebo FP or CAPOX n=789**
OS		
Number (%) of patients with event	603 (76)	666 (84)
Median in months* (95% CI)	12.9 (11.9,14.0)	11.5 (10.6,12.1)
Hazard ratio† (95% CI)	0.78 (0.70, 0.87)	
p-Value (stratified log-rank)‡	<0.0001	
PFS		
Number (%) of patients with event	572 (72)	608 (77)
Median in months* (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)
Hazard ratio† (95% CI)	0.76 (0.67, 0.85)	
p-Value (stratified log-rank)‡	<0.0001	
Objective Response Rate		
ORR§ (95% CI)	51% (47.7, 54.8)	42% (38.5, 45.5)
Complete response rate	9%	6%
Partial response rate	42%	36%
Difference (95% CI)	9% (4.4, 14.1)	
p-Value¶	0.00009	
Response Duration	n=405	n=331
Median in months (range)	8.0 (1.2+ - 41.5+)	5.7 (1.3+ - 34.7+)
% with duration ≥ 12 months*	39%	26%
% with duration ≥ 24 months*	27%	13%

* Based on Kaplan-Meier estimation

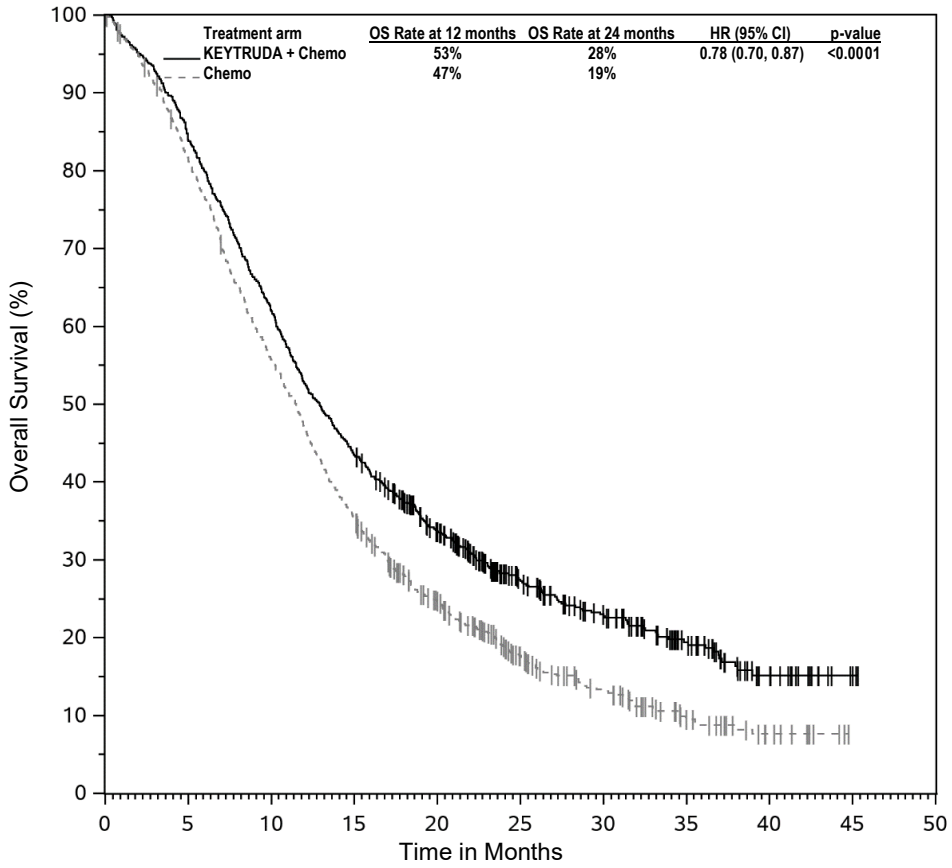
† Based on the stratified Cox proportional hazard model

‡ 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 & Nurminen method

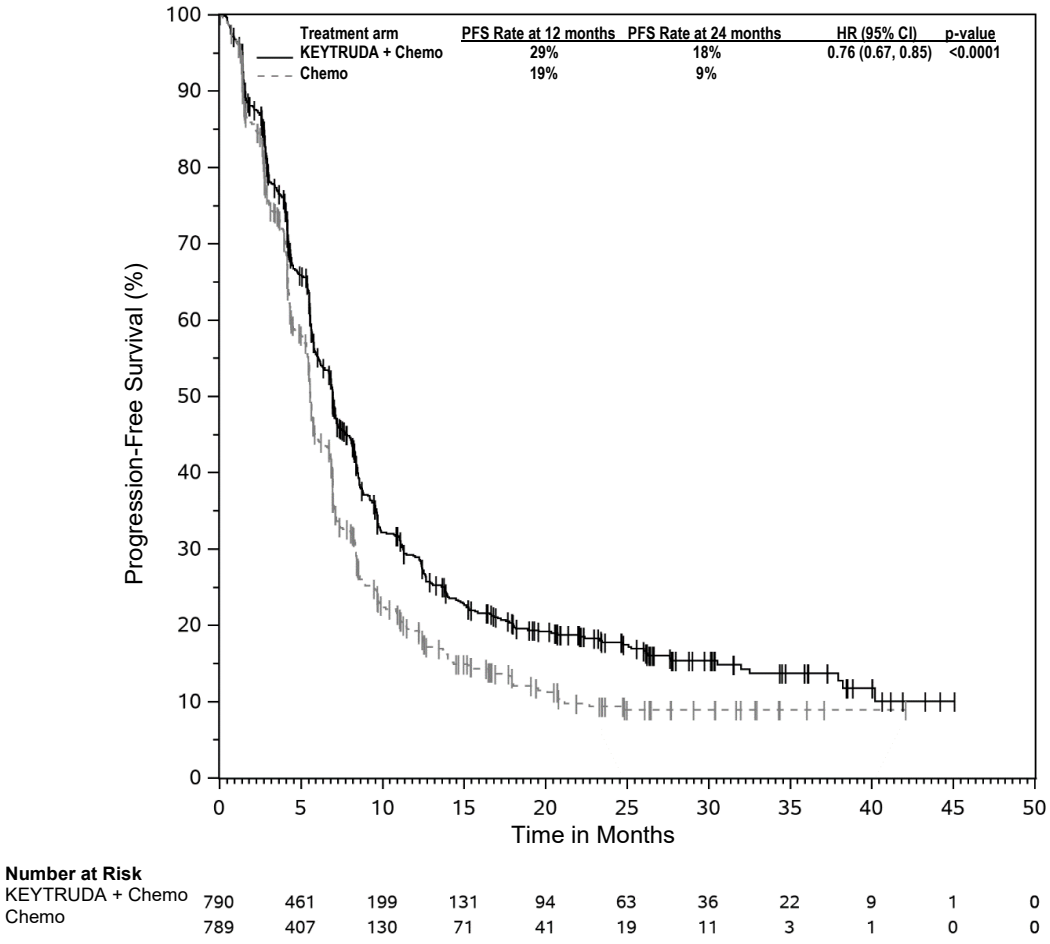
Figure 30: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859



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 31: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-859



KEYNOTE-811: First-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (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. Randomization 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 randomized (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 cycle:

- 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). Placebo was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.

Treatment with KEYTRUDA, 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. Treatment was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumor status was performed every 6 weeks.

Among the 698 patients randomized in KEYNOTE-811, 594 (85%) had tumors that expressed PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. The population characteristics of these 594 patients were: 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 tumors that were not MSI-H, 1% (n=8) had tumors 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 first interim analysis conducted on the first 264 patients randomized in the overall population (133 patients in the KEYTRUDA arm and 131 in the placebo arm), a statistically significant improvement was observed in the objective response rate (74.4% vs 51.9%, representing a 22.7% difference; 95% CI (11.2, 33.7); p-Value 0.00006).

At the second interim analysis in the overall population, a statistically significant improvement in PFS (HR 0.72; 95% CI 0.60, 0.87; p-Value 0.0002) was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. At the time of this analysis in the overall population, there was no statistically significant difference with respect to OS.

Efficacy results at the second interim analysis for the pre-specified subgroup of patients whose tumors expressed PD-L1 with a CPS ≥1 are summarized in Table 33 and Figures 32 and 33.

Table 33: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥1

Endpoint	**KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=298**	**Placebo Trastuzumab Fluoropyrimidine and Platinum 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 (61.8%)

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 rate	14%	10%
Partial response rate	59%	49%
Difference (95% CI) §	15% (7, 22)	
p-Value§	0.00008	
Response Duration	n=218	n=173
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 the unstratified Cox proportional hazard model

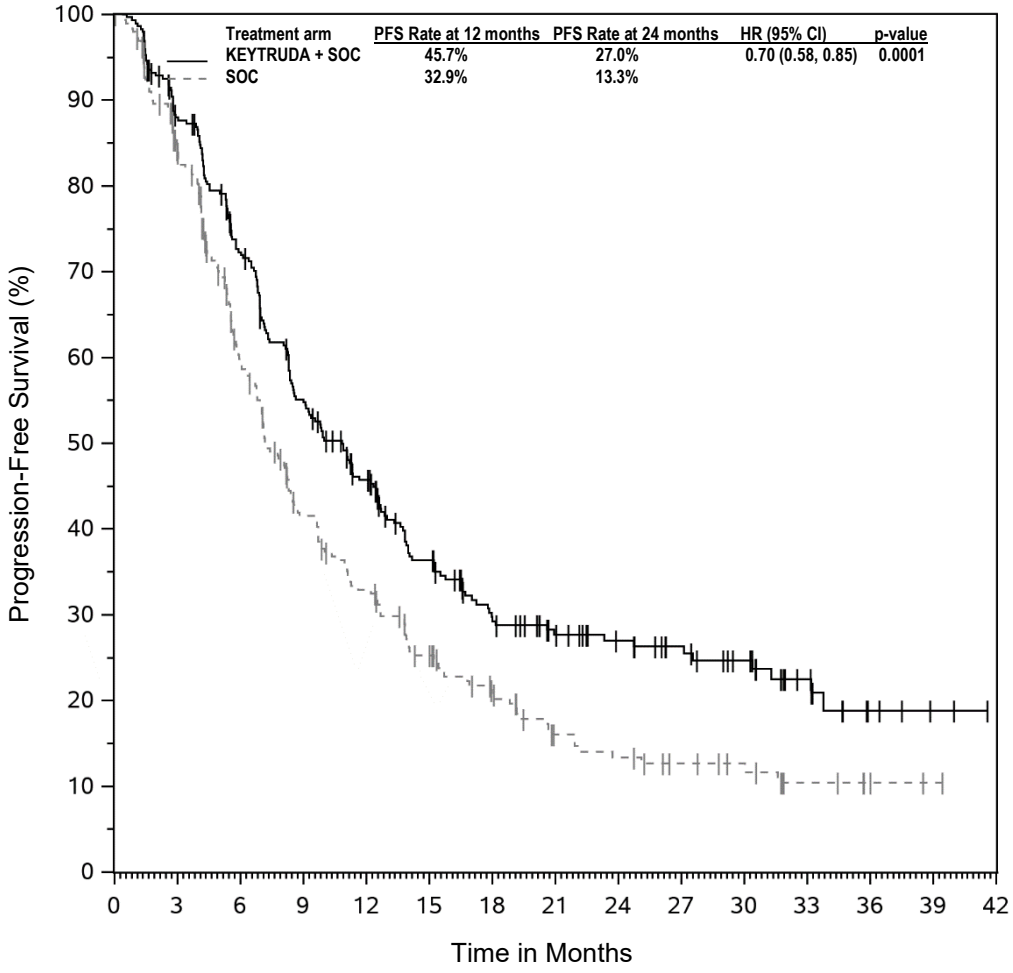
† Based on unstratified log-rank test; p-value is nominal p-value

‡ Response: Best objective response as confirmed complete response or partial response

§ Based on unstratified Miettinen and Nurminen method; p-value is nominal p-value

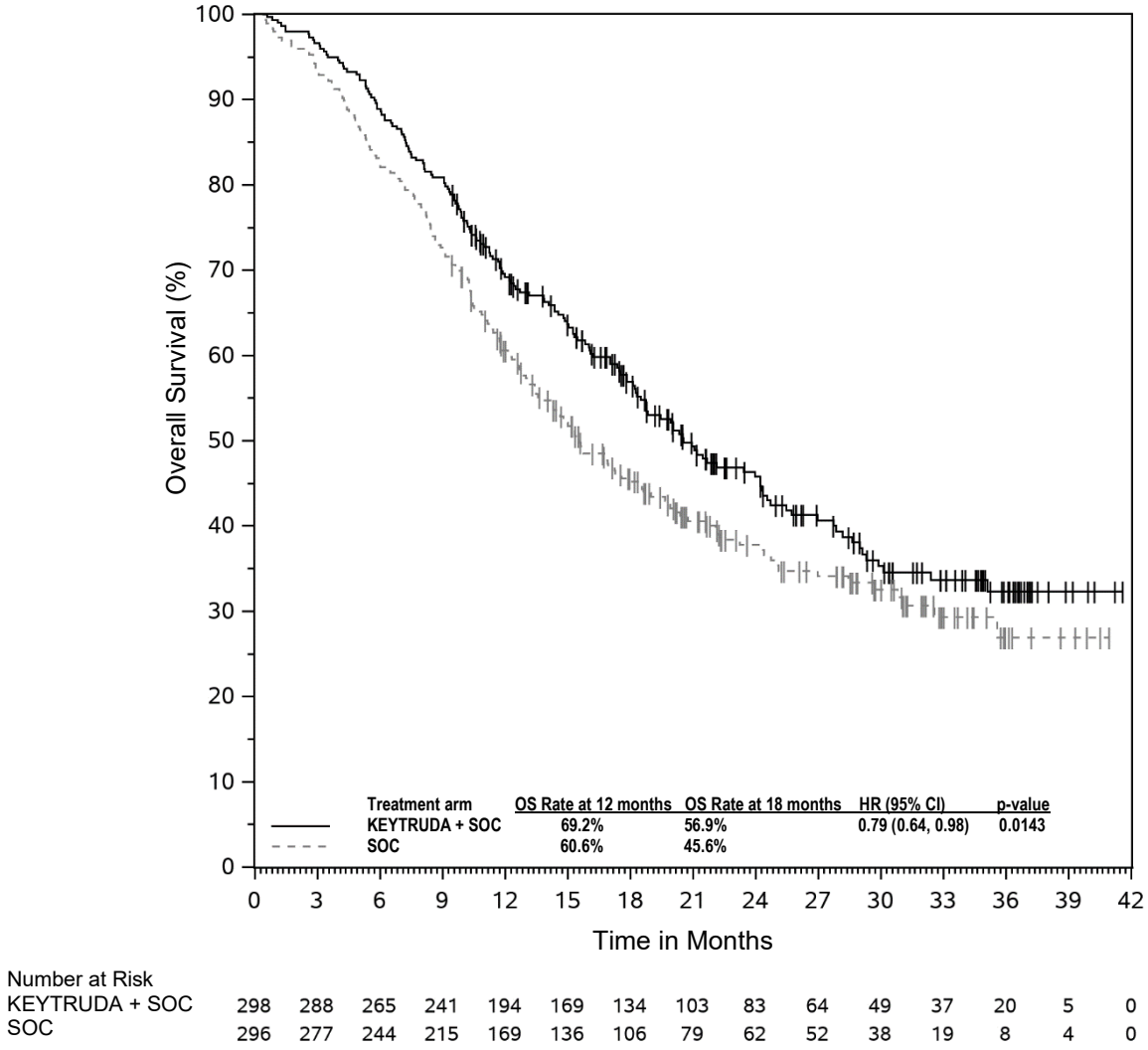
¶ Based on Kaplan-Meier estimation

Figure 32: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



Number at Risk															
KEYTRUDA + 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 33: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



Renal Cell Carcinoma

KEYNOTE-426: Controlled trial of combination therapy with axitinib for first-line treatment of patients with advanced RCC

The efficacy of KEYTRUDA in combination with axitinib was investigated in a randomized, multicenter, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC, regardless of PD-L1 tumor status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Randomization was stratified by 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 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 KEYTRUDA and axitinib continued until RECIST 1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. 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. Chemistry and hematology laboratory tests were performed at each cycle.

Among the 861 patients in KEYNOTE-426 (432 patients in the KEYTRUDA combination arm and 429 in the sunitinib arm), baseline characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 99.9% had a Karnofsky Performance Score (KPS) of ≥70%; patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time for 432 patients treated with KEYTRUDA and axitinib was 13.2 months (range: 0.1 – 21.5 months). Table 34 summarizes key efficacy measures. Improvements in OS, PFS and ORR were shown consistently across all tested subgroups, including subgroups by IMDC risk category and PD-L1 tumor expression status.

Table 34: Response to KEYTRUDA and Axitinib in Patients with Advanced RCC in KEYNOTE-426

Endpoint	KEYTRUDA with axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	0.00005	
12-month OS rate (95% CI)	90% (86, 92)	78% (74, 82)
18-month OS rate (95% CI)	82% (77, 86)	72% (66, 77)
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†	0.00012	
ORR		
Overall response rate‡ (95% CI)	59% (54, 64)	36% (31, 40)
Complete response	6%	2%
Partial response	53%	34%
p-Value§	<0.0001	
Response Duration		
Median in months (range)	Not reached (1.4+, 18.2+)	15.2 (1.1+, 15.4+)
Number (%¶) of patients with duration ≥6 months	161 (88%)	84 (81%)

Number (%¶) of patients with duration ≥12 months	58 (71%)	26 (62%)

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test.

‡ Based on patients with a best overall response as confirmed complete or partial response

§ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

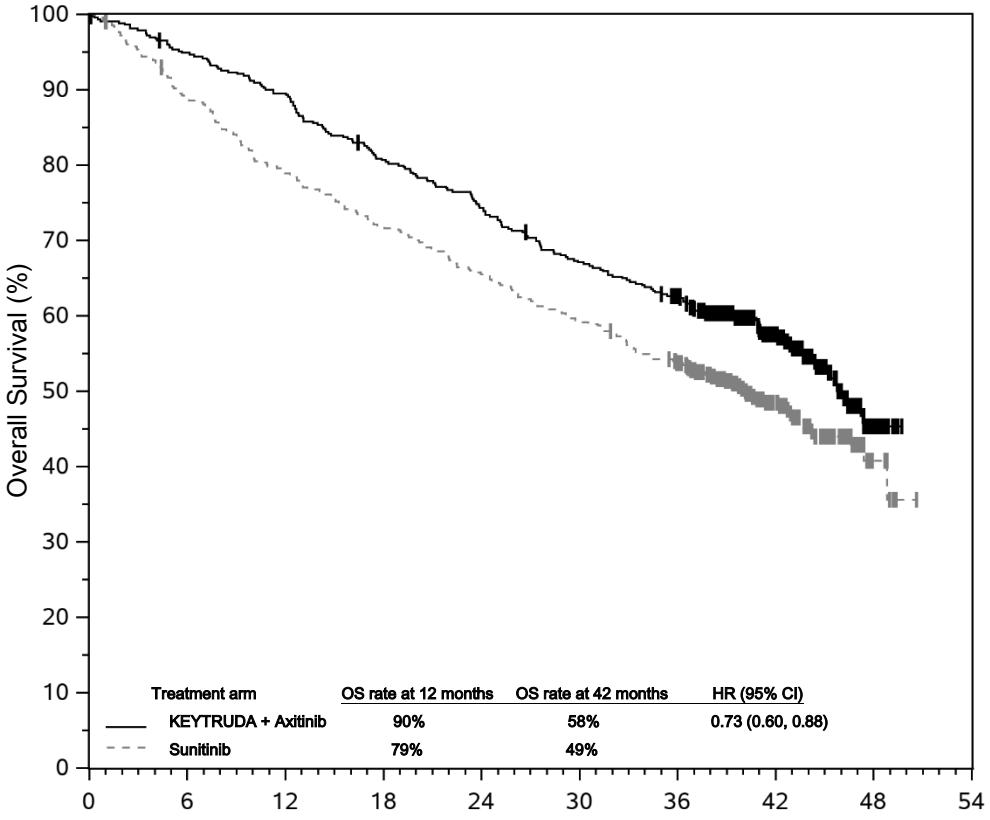
¶ Based on Kaplan-Meier estimation

NA = not available

The protocol-specified final OS analysis was performed at a median duration of follow-up of 37.7 months after 418 patient events (193 in the KEYTRUDA and axitinib arm and 225 in the sunitinib arm). Median OS was 45.7 months (95% CI: 43.6, NA) in the KEYTRUDA and axitinib arm and 40.1 months (95% CI: 34.3, 44.2) in the sunitinib arm. The OS HR was 0.73 (95% CI: 0.60, 0.88). The 12-month OS rates were 90% (95% CI: 86, 92) in the KEYTRUDA and axitinib arm and 79% (95% CI: 75, 83) in the sunitinib arm. The 24-month OS rates were 74% (95% CI: 70, 78) in the KEYTRUDA and axitinib arm and 66% (95% CI: 61, 70) in the sunitinib arm. The 36-month OS rates were 63% (95% CI: 58, 67) in the KEYTRUDA and axitinib arm and 54% (95% CI: 49, 58) in the sunitinib arm. The 42-month OS rates were 58% (95% CI: 53, 62) in the KEYTRUDA and axitinib arm and 49% (95% CI: 44, 53) in the sunitinib arm. At final analysis, a PFS analysis was performed based on 587 patient events (286 in the KEYTRUDA and axitinib arm and 301 in the sunitinib arm). The median PFS was 15.7 months (95% CI: 13.6, 20.2) in the KEYTRUDA and axitinib arm and 11.1 months (95% CI: 8.9, 12.5) in the sunitinib arm. The PFS HR was 0.68 (95% CI: 0.58, 0.80).

The ORR at the final analysis was 60% in the KEYTRUDA and axitinib arm and 40% in the sunitinib arm. The median duration of response was 23.6 months (range: 1.4+ to 43.4+) in the KEYTRUDA and axitinib arm and 15.3 months (range: 2.3 to 42.8+) in the sunitinib arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 71%, 59%, 49%, and 45% at 12, 18, 24, and 30 months, respectively, in patients with confirmed response in the KEYTRUDA and axitinib arm, vs. 62%, 46%, 37%, and 32% in patients with confirmed response in the sunitinib arm.

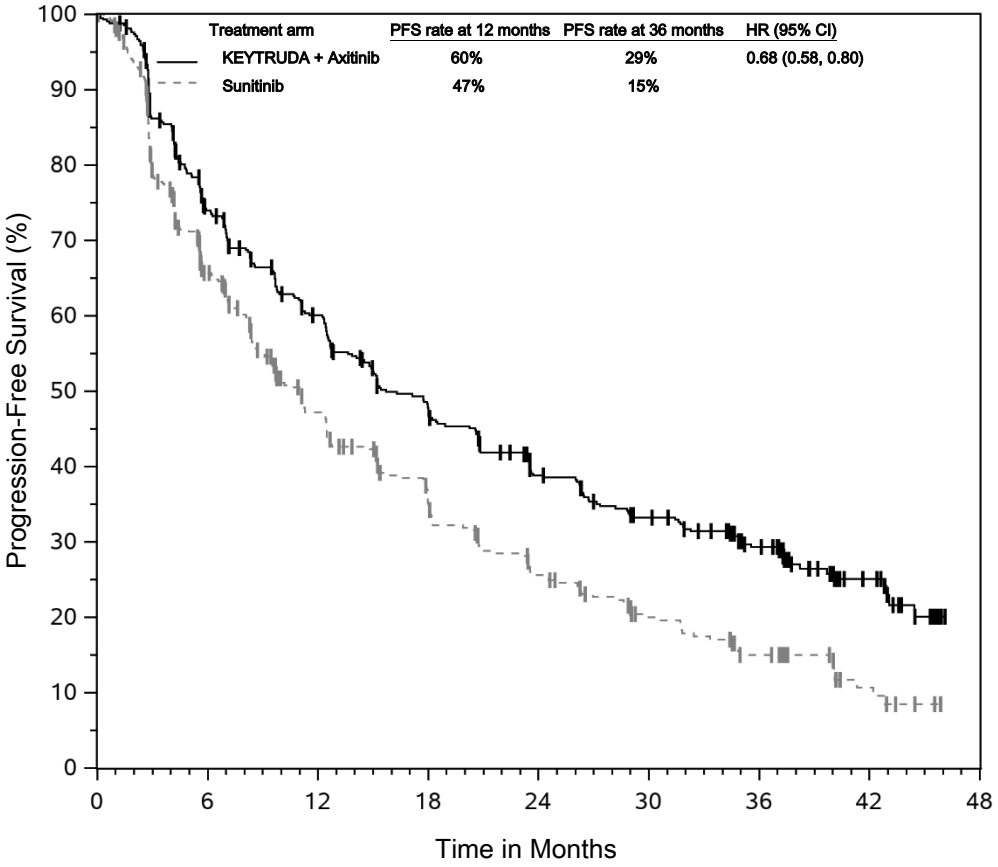
Figure 34: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat population)



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

Figure 35: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat population)



Number at Risk									
KEYTRUDA + Axitinib	432	298	233	180	136	110	80	28	0
Sunitinib	429	244	155	107	72	47	28	10	0

KEYNOTE-581: Controlled trial of combination therapy with lenvatinib for first-line treatment of patients with advanced RCC

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581, 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 as determined by the investigator and confirmed by BICR using RECIST 1.1. 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.

Among the 1069 patients in KEYNOTE-581 (355 patients in the KEYTRUDA with lenvatinib arm, 357 patients in the lenvatinib with everolimus arm, and 357 patients in the sunitinib arm), 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 IMDC risk categories was 33% favorable, 56% intermediate and 10% poor, and 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 primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The trial demonstrated statistically significant improvements in PFS, OS, and ORR in patients randomized to KEYTRUDA in combination with lenvatinib compared with sunitinib. The median overall survival follow-up time was 26.6 months. Pre-specified interim analysis efficacy results for KEYNOTE-581 are summarized in Table 35. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumor expression status.

Table 35: Efficacy Results in KEYNOTE-581

Endpoint	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=355	Sunitinib n=357
PFS		
Number of patients with event (%)	160 (45%)	205 (57%)
Median 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	
OS		
Number of patients with event (%)	80 (23%)	101 (28%)
Median 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	
12-month OS rate	91 (88, 94)	80 (76, 84)
18-month OS rate	87 (83, 90)	74 (69, 79)
24-month OS rate	79 (74, 83)	70 (65, 75)
Objective Response Rate		
ORR‡ (95% CI)	71% (66, 76)	36% (31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value§	<0.0001	
Response Duration¶		
Median in months (range)	26 (1.6+, 36.8+)	15 (1.6+, 33.2+)

* Based on the stratified Cox proportional hazard model

† Two-sided p-Value based on stratified log-rank test

‡ Response: Best objective response as confirmed complete response or partial response

§ Nominal p-Value. 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 KEYTRUDA plus lenvatinib with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), p-Value <0.0001)

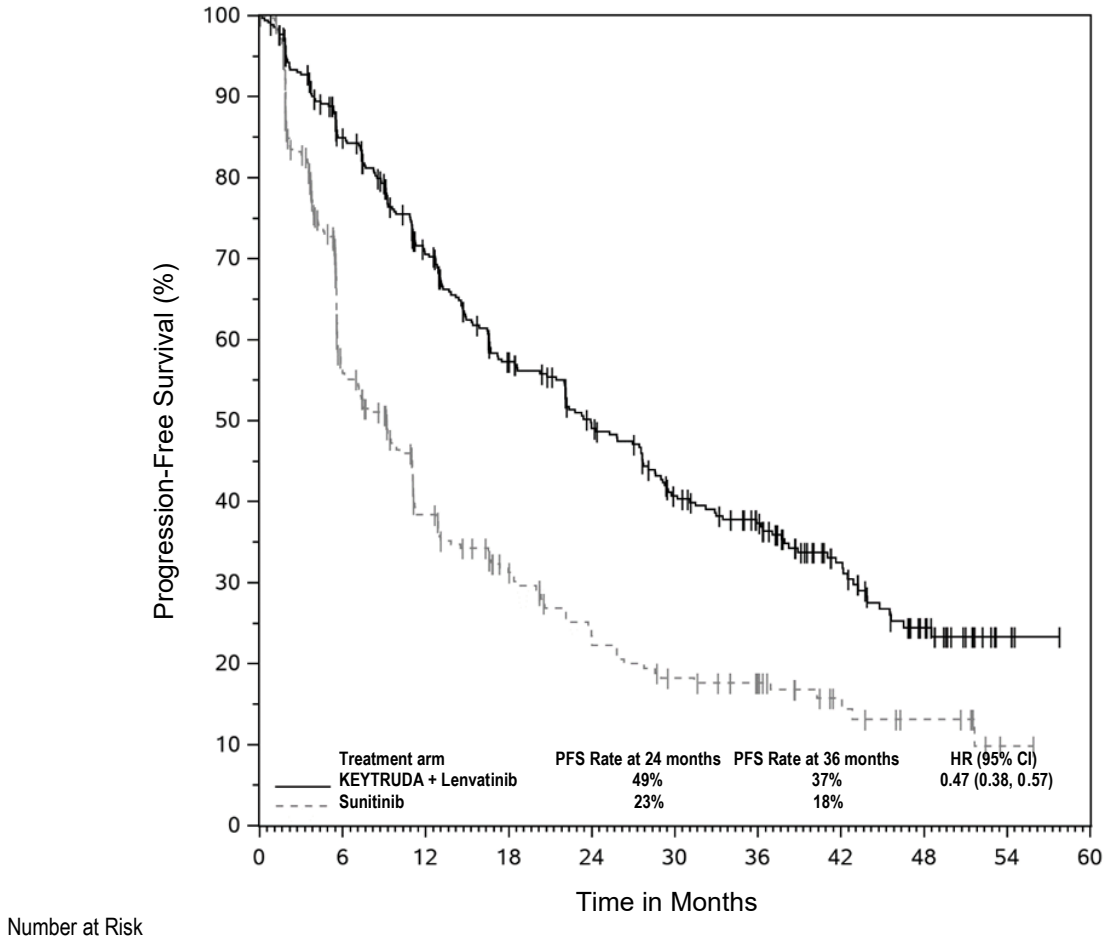
¶ Based on Kaplan-Meier estimates

NR = not reached

At the protocol-specified final analysis, median follow-up was 49.4 months. The PFS analysis was performed with 207 patient events for KEYTRUDA in combination with lenvatinib and 214 patient events for sunitinib. The median PFS was 23.9 months (95% CI: 20.8, 27.7) for KEYTRUDA in combination with lenvatinib and 9.2 months (95% CI: 6.0, 11.0) for sunitinib. The PFS HR was 0.47 (95% CI: 0.38, 0.57, nominal p<0.0001). At the final OS analysis there were 149 patients events for KEYTRUDA in combination with lenvatinib and 159 patients events for sunitinib. Median OS was 53.7 months (95% CI: 48.7, NE) for KEYTRUDA in combination with lenvatinib and 54.3 months (95% CI: 40.9, NE) for sunitinib. The OS HR was 0.79 (95% CI: 0.63, 0.99; nominal p<0.0424). The OS analysis was not adjusted to account for subsequent therapies, in which 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the pembrolizumab plus lenvatinib arm received subsequent systemic anti-PD-1/PD-L1 therapy. OS may be confounded by the difference in subsequent therapies. See Figures 36 and 37.

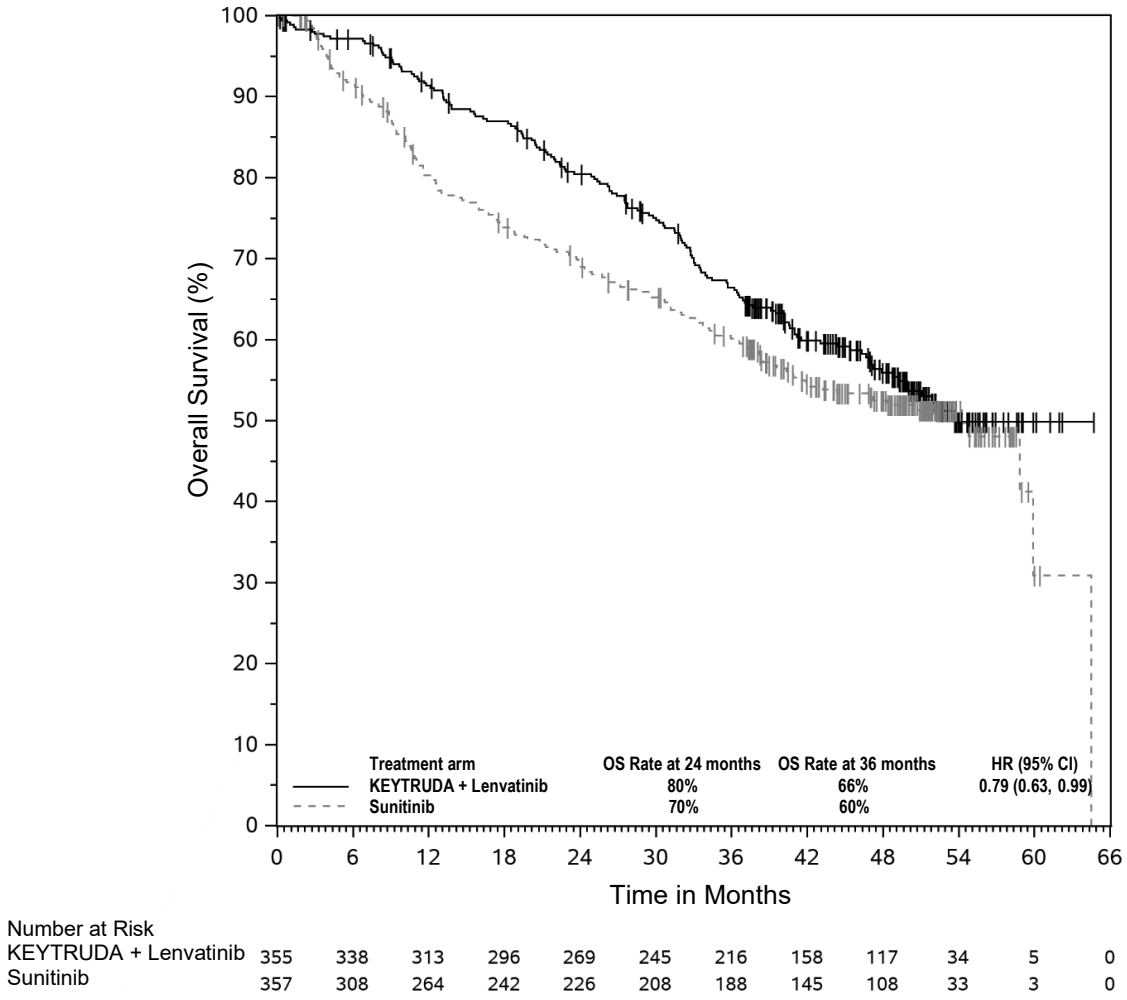
The ORR was 71% for KEYTRUDA in combination with lenvatinib and 37% for sunitinib. The complete response rates were 18% for KEYTRUDA in combination with lenvatinib and 5% for sunitinib. The median duration of response was 26.7 months (range: 1.64+, 55.92+) for KEYTRUDA in combination with lenvatinib and 14.7 months (range: 1.64+, 54.08+) for sunitinib. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 56% and 41% at 24 and 36 months or longer in patients who received KEYTRUDA in combination with lenvatinib vs. 32% and 24% in patients who received sunitinib.

Figure 36: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-581



Number at Risk											
KEYTRUDA + 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 37: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-581



Patient-reported outcomes (PROs) were assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 and Kidney Cancer Symptom Index (FKSI-DRS). From baseline to a mean follow-up time of 46 weeks, patients treated with pembrolizumab in combination with lenvatinib had better physical functioning, fatigue, dyspnea, and constipation scores compared to the sunitinib group. Compared to sunitinib, pembrolizumab in combination with lenvatinib showed a more than 12 week delay in median time to worsening in global health status (GHS), physical functioning and patient reported symptoms with no subsequent recovery: EORTC QLQ-C30 GHS (114 vs. 75 weeks, HR=0.6 [95% CI: 0.47, 0.77]), physical functioning (134 vs. 78 weeks, HR=0.52 [95% CI: 0.41, 0.67]), fatigue (110 vs. 59 weeks, HR=0.54 [95% CI: 0.43, 0.67]), insomnia (156 vs. 126 weeks, HR=0.63 [95% CI: 0.47. 0.85]), dyspnea (153 vs. 126 weeks, HR=0.56 [95% CI: 0.41, 0.76]), nausea and vomiting (147 vs. 131 weeks,

HR=0.53 [95% CI: 0.39, 0.74]), pain (119 vs. 105 weeks, HR=0.68 [95% CI: 0.53, 0.87]) and FKSI-DRS (134 vs. 117 weeks, HR=0.7 [95% CI: 0.53, 0.92]). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-564: Placebo-controlled study for the adjuvant treatment of patients with resected RCC

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicenter, randomized, double-blind, placebo-controlled study 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 with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year, until disease recurrence, or until unacceptable toxicity. Randomization was stratified by metastasis status (M0, M1 NED), within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Patients underwent imaging every 12 weeks for the first 2 years from randomization, 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; 84% 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 KEYTRUDA and placebo arms.

The primary efficacy outcome measure was investigator-assessed DFS. The key secondary outcome measure was OS. The study demonstrated statistically significant improvements in DFS and OS for patients randomized to the KEYTRUDA arm compared with placebo. Generally consistent results were observed across pre-specified subgroups. Efficacy results are summarized in Table 36 and Figures 38 and 39.

Table 36: 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§	
12-month DFS rate (95% CI)	86% (82, 89)	76% (72, 80)
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)
OS†		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR	NR
Hazard ratio (95% CI)‡	0.62 (0.44, 0.87)	
p-Value	0.0024§	
12-month OS rate (95% CI)	99% (97, 99)	98% (96, 99)
24-month OS rate (95% CI)	96% (94, 98)	94% (91, 96)

36-month OS rate (95% CI)	94% (91, 96)	90% (86, 92)
48-month OS rate (95% CI)	91% (88, 93)	86% (83, 89)

* Median follow-up time was 23.9 months (range: 2.5 to 41.5 months).

† Median follow-up time was 55.8 months (range: 2.5 to 74.5 months).

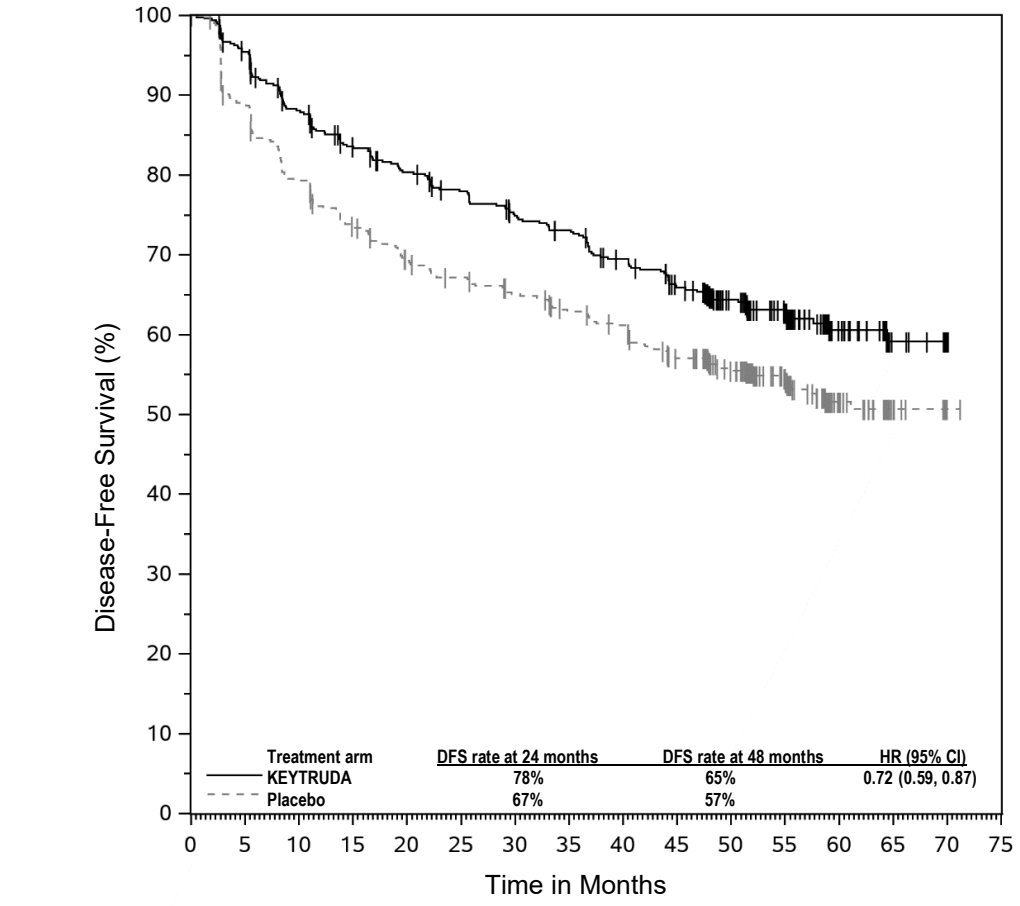
‡ Based on the stratified Cox proportional hazard model

§ Based on stratified log-rank test

NR = not reached

At a pre-specified interim analysis (median follow-up time was 55.8 months (range: 2.5 to 74.5 months)), the updated DFS HR was 0.72 (95% CI: 0.59, 0.87). The updated 12-month DFS rates were 86% (95% CI: 82, 88) in the KEYTRUDA arm and 76% (95% CI: 72, 80) in the placebo arm. The updated 24-month DFS rates were 78% (95% CI: 74, 82) in the KEYTRUDA arm and 67% (95% CI: 63, 71) in the placebo arm. The 36-month DFS rates were 72% (95% CI: 68, 76) in the KEYTRUDA arm and 63% (95% CI: 58, 67) in the placebo arm. The 48-month DFS rates were 65% (95% CI: 60, 69) in the KEYTRUDA arm and 57% (95% CI: 52, 61) in the placebo arm.

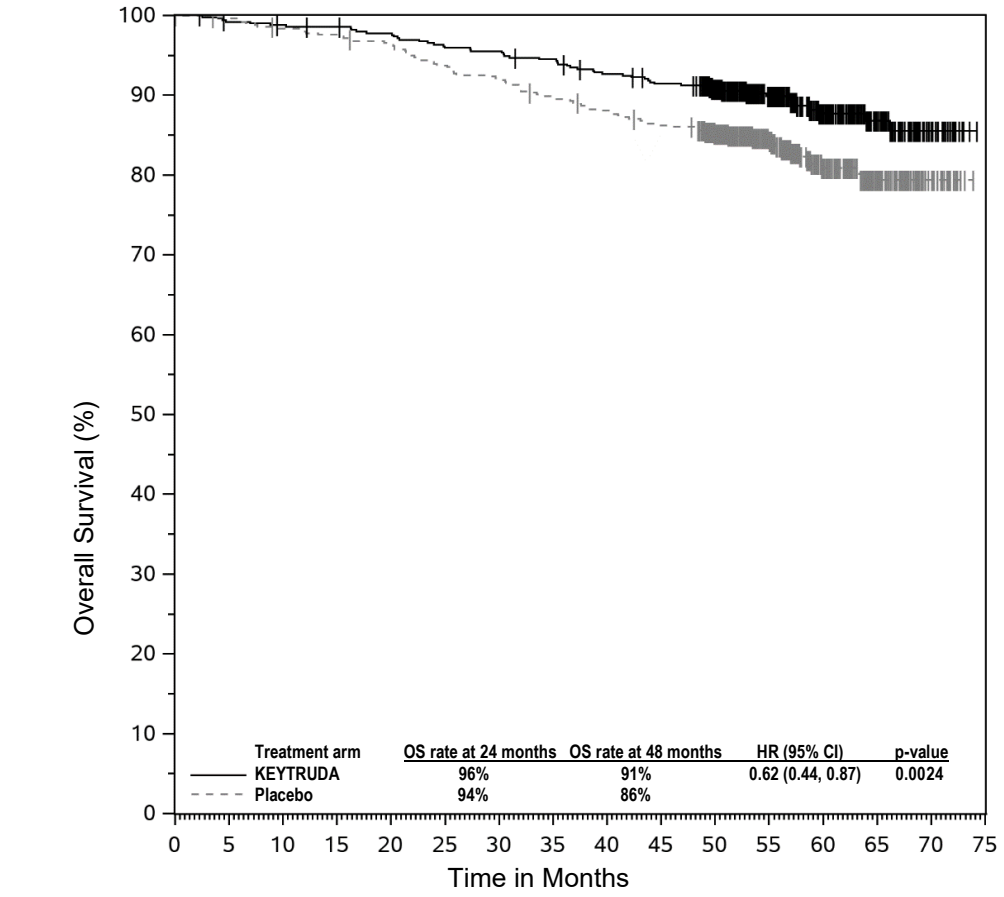
Figure 38: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-564



Number at Risk

KEYTRUDA	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 39: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-564



Number at Risk

KEYTRUDA	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

Classical Hodgkin Lymphoma

KEYNOTE-204: Controlled study in patients with relapsed or refractory classical Hodgkin Lymhoma (cHL)

KEYNOTE-204 was a randomized, open-label, active-controlled trial 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 trial. Randomization was stratified by prior auto-SCT (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 randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks
- Brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Disease assessment was performed every 12 weeks. The major efficacy outcome measures were PFS and ORR as assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

Among KEYNOTE-204 patients, the baseline characteristics were median age 35 years (16% age 65 or older); 57% male; 77% White; and 61% and 38% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 2 (range 1 to 11). Forty-two percent were refractory to the last prior therapy and 29% had primary refractory disease. Thirty-seven percent had undergone prior auto-HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

The median follow-up time for 151 patients treated with KEYTRUDA was 24.9 months (range: 1.8 to 42.0 months). Efficacy results are summarized in Table 37.

Table 37: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

Endpoint	**KEYTRUDA 200 mg/kg 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% (57.4, 73.1)	54% (46.0, 62.3)
Complete response	25%	24%
Partial response	41%	30%
p-Value§	0.0225	
Response Duration		
Median in months (range)	20.7 (0.0+, 33.2+)	13.8 (0.0+, 33.9+)
Number (%¶) of patients with duration ≥ 6 months	66 (80%)	34 (60%)
Number (%¶) of patients with duration ≥ 12 months	48 (62%)	23 (50%)
Number (%¶) of patients with duration ≥ 24 months	11 (47%)	7 (43%)

* Based on the stratified Cox proportional hazard model

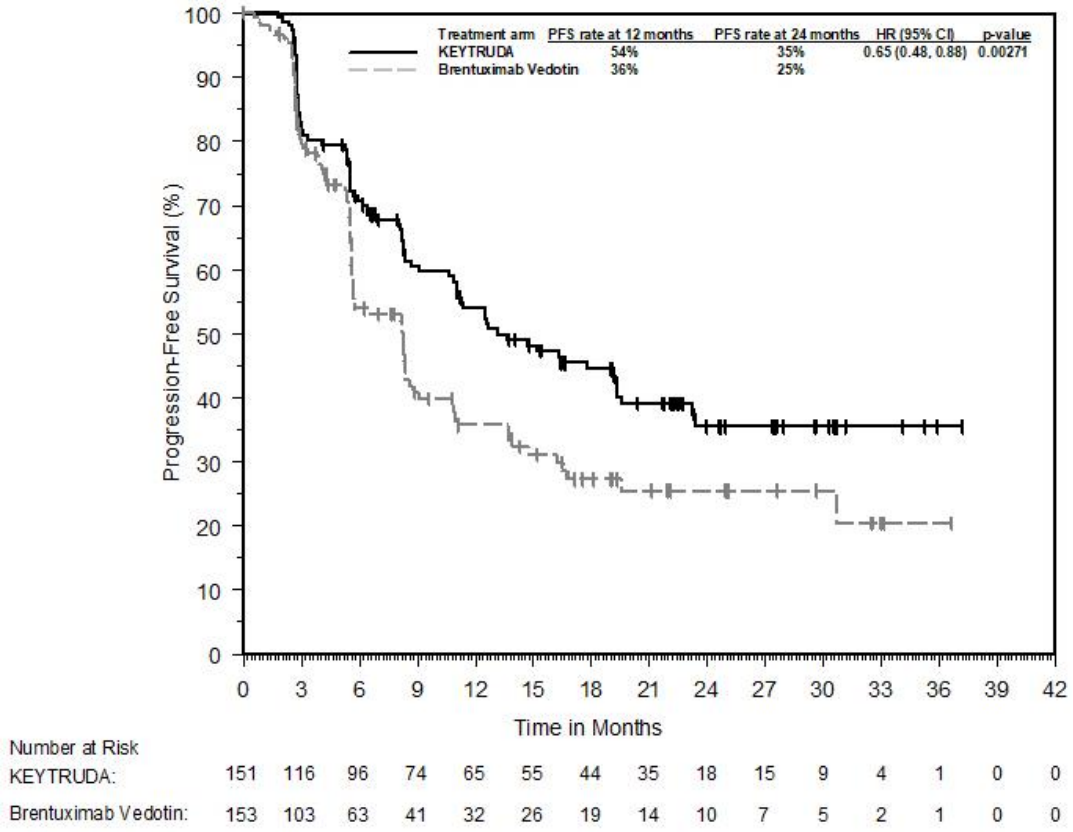
† Based on stratified log-rank test

‡ Based on patients with best overall response as complete response or partial response

§ Based on Miettinen and Nurminen method stratified by prior auto-SCT and disease status

¶ Based on Kaplan-Meier estimation

Figure 40: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204



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 BV (HR 0.40; 95% CI: 0.22-0.74). Over 24 weeks of follow-up, patients treated with pembrolizumab had an improvement in global health status/QoL compared to BV which showed a decline (difference in Least Square (LS) means = 8.60; 95% CI: 3.89, 13.31; nominal two-sided p=0.0004). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Colorectal Cancer

KEYNOTE-177: Controlled trial for first-line treatment of patients with MSI-H or dMMR CRC

The efficacy of KEYTRUDA was investigated in KEYNOTE-177, 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 primary efficacy outcome measures were PFS assessed by BICR according to RECIST v1.1 and OS. Secondary 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. 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 trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy at an interim analysis. There

was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis, with an additional 12 months of follow-up, in which 60% 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 was 38.1 months (range: 0.2 to 58.7 months). Table 38 and Figures 41 and 42 summarize the key efficacy measures for KEYNOTE-177.

Table 38: Efficacy Results for First-line Treatment in Patients with MSI-H 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†	0.0002	
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)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Response Duration		
Median in months (range)	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)
% of patients with duration ≥ 6 months¶	97%	88%
% of patients with duration ≥ 12 months¶	85%	44%
% of patients with duration ≥ 24 months¶	83%	35%

* Based on Cox regression model

† Based on log-rank test (compared to a significance level of 0.0117)

‡ Based on final analysis

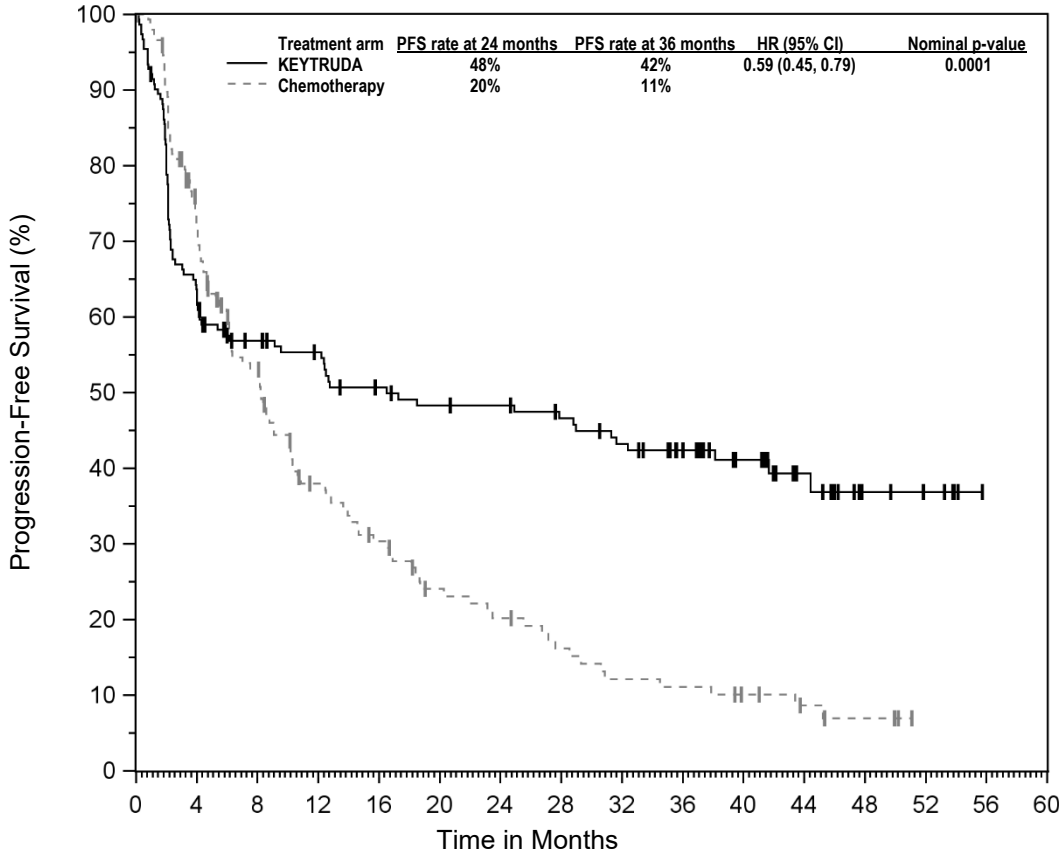
§ Not statistically significant after adjustment for multiplicity

¶ Based on Kaplan-Meier estimation

NR=not reached

At the final analysis, there were a total of 203 PFS events (86 for KEYTRUDA; 117 for chemotherapy). The median PFS was 16.5 months (95% CI: 5.4, 38.1) for the KEYTRUDA arm and 8.2 months (95% CI: 6.1, 10.2) for the chemotherapy arm. The PFS HR vs. chemotherapy was 0.59 (95% CI: 0.45, 0.79, nominal p=0.0001) (Figure 41). The ORR at the final analysis was 45% for the KEYTRUDA arm and 33% for the chemotherapy arm. The median duration of response was not reached (range: 2.3+, 53.5+) for the KEYTRUDA arm and 10.6 months (range: 2.8, 48.3+) for the chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 84% at 24 months or longer in the KEYTRUDA arm vs. 34% in the chemotherapy arm.

Figure 41: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)*

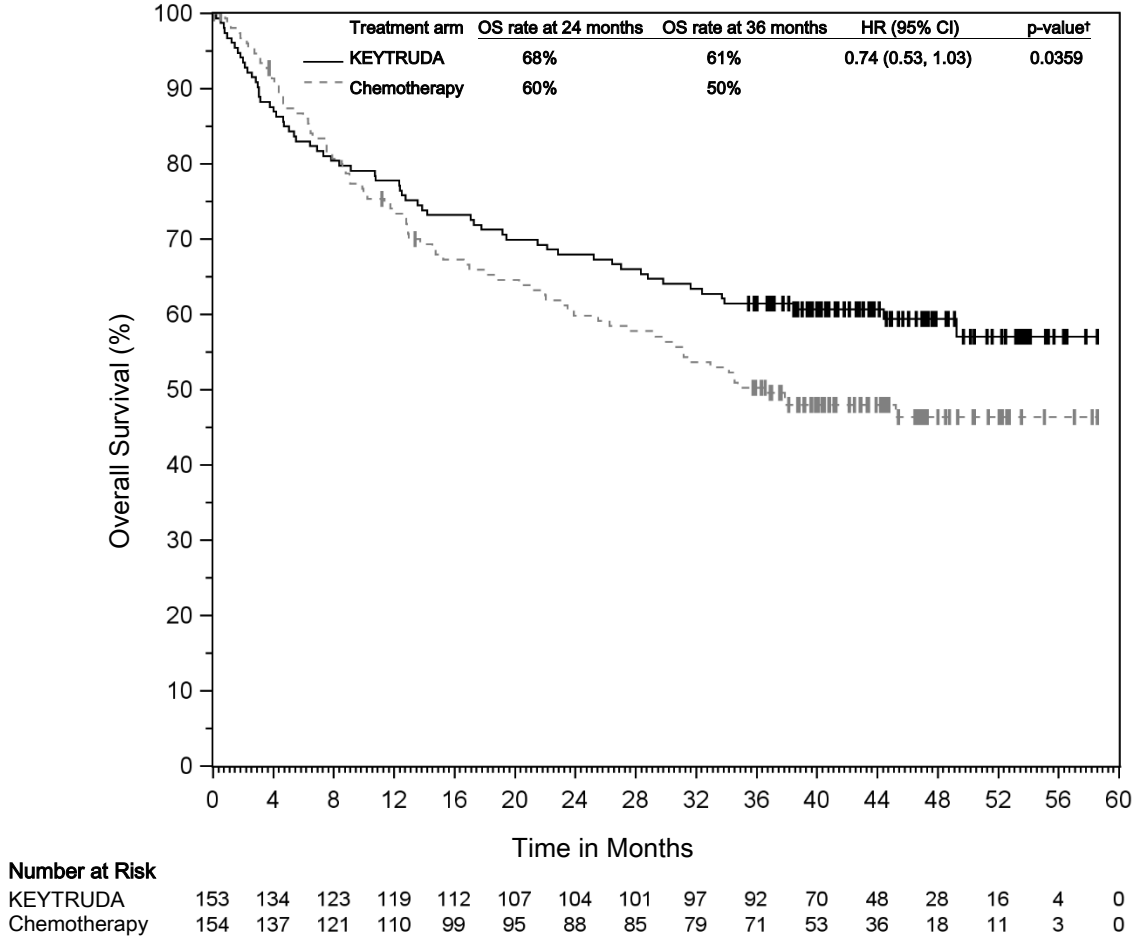


Number at Risk

KEYTRUDA	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

* At the time of the protocol-specified final analysis.

Figure 42: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)*



* At the time of the protocol-specified final analysis.

† Not statistically significant after adjustment for multiplicity.

Exploratory analyses of patient-reported outcomes (PROs) using EORTC QLQ-C30 show improvement in global health status/quality of life, functioning (i.e., physical, role, social) and fatigue in patients treated with KEYTRUDA compared to a decline for patients treated with chemotherapy at pre-specified Week 18. Improvements from baseline in global health status/quality of life continued through Week 45 for patients treated with KEYTRUDA. In addition, a prolonged time to deterioration in global health status/QoL (HR 0.61; 95% CI: 0.38-0.98), physical (HR 0.50; 95% CI: 0.32-0.81) and social functioning (HR 0.53; 95% CI: 0.32-0.87), and fatigue (HR 0.48; 95% CI: 0.33-0.69) was observed for patients treated with KEYTRUDA compared to chemotherapy. These

results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Triple-Negative Breast Cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC

The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide, given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in Study KEYNOTE-522, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were 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), regardless of tumor 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. 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 treatment arms; all study medications were administered via intravenous infusion.

- **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 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 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, 9 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 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 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, 9 cycles of placebo every 3 weeks were administered.

Treatment with KEYTRUDA 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.

The major 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

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 measure was OS.

A total of 1174 patients were randomized: 784 patients to the KEYTRUDA arm and 390 patients to the placebo arm. 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; 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.

The trial demonstrated a statistically significant improvement in pCR and EFS at a pre-specified analysis for patients randomized to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with chemotherapy followed by placebo alone. At the time of EFS analysis, OS results were not yet mature (45% of the required events for final analysis). However, the data showed an improvement in OS that favored the KEYTRUDA arm over the placebo arm. At a pre-specified interim analysis, the median follow-up time for 784 patients treated with KEYTRUDA was 37.8 months (range: 2.7-48 months). Efficacy results are summarized in Table 39 and Figure 43.

Table 39: Efficacy Results in Patients with High-Risk Early-Stage TNBC in KEYNOTE-522

Endpoint	KEYTRUDA with chemotherapy/KEYTRUDA	Placebo with chemotherapy/Placebo
pCR (ypT0/Tis ypN0)*	**n=401**	**n=201**
Number of patients with pCR	260	103
pCR Rate (%), (95% CI)	64.8 (59.9, 69.5)	51.2 (44.1, 58.3)
Treatment difference (%) estimate (95% CI)†	13.6 (5.4, 21.8)	
p-Value	0.00055	

EFS‡	n=784	n=390
Number of patients with event (%)	123 (16%)	93 (24%)
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	

* Based on a pre-specified pCR interim analysis (compared to a significance level of 0.003)

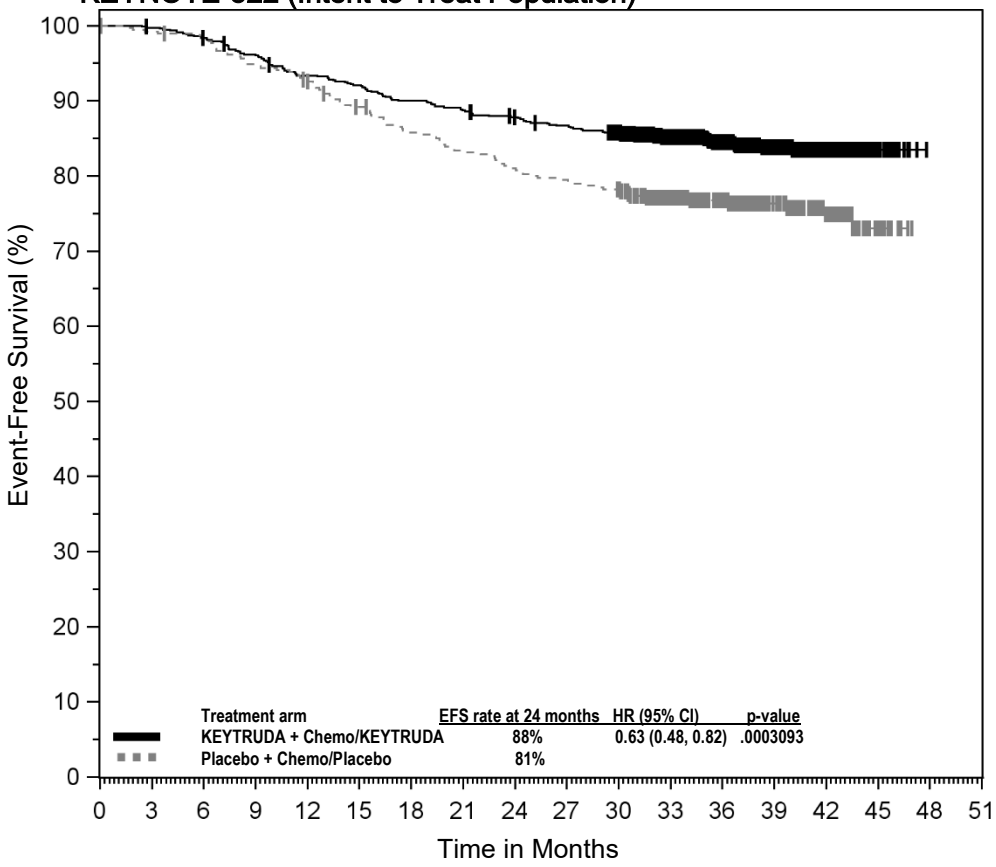
† Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin

‡ Based on 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, tumor size, and choice of carboplatin

¶ Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin

Figure 43: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



Number at Risk

KEYTRUDA + Chemo/KEYTRUDA:	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

The impact of the addition of KEYTRUDA to chemotherapy on health-related quality of life was assessed using the EORTC QLQ-C30. Over 21 weeks of follow up, the Least Square (LS) mean score change in the QLQ-C30 global health status/QoL scale was -11.24 (-12.82, -9.66) in patients treated with KEYTRUDA in combination with chemotherapy and -10.20 (-12.30, -8.10) in patients treated with placebo in combination with chemotherapy as neoadjuvant treatment [difference in LS means: -1.04; 95% CI: -3.46, 1.38]. Over 24 weeks of follow up, the LS mean score change in the global health status/QoL scale was 2.47 (1.05, 3.88) in patients treated with KEYTRUDA and 2.88 (1.05, 4.71) in patients treated with placebo as adjuvant treatment [difference in LS means: -0.41 (-2.60, 1.77)].

KEYNOTE-355: Controlled study of combination therapy in TNBC patients

The efficacy of KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin was investigated in Study KEYNOTE-355, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, and which had not been previously treated with chemotherapy. 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. Randomization was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS ≥1 vs. CPS <1) based on 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 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 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 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 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Treatment with KEYTRUDA or placebo continued until RECIST 1.1-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 Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter.

The major efficacy outcome measures were OS and PFS as assessed by BICR using RECIST 1.1, in patients with tumor PD-L1 expression CPS ≥10. Additional efficacy outcome measures were ORR, DOR, and DCR (stable disease for at least 24 weeks, or

complete response, or partial response) in patients with tumor PD-L1 expression CPS ≥10 as assessed by BICR using RECIST 1.1.

A total of 847 patients were randomized: 566 patients to the KEYTRUDA arm and 281 patients to the placebo arm. The study population characteristics 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 the patients had tumor PD-L1 expression defined as CPS ≥1 and 38% had tumor PD-L1 expression CPS ≥10.

In KEYNOTE-355, there was a statistically significant improvement in OS and PFS in patients with tumor PD-L1 expression CPS ≥10 randomized to KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin compared with patients randomized to placebo in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin. The trial also demonstrated a clinically meaningful improvement in ORR and DoR.

Efficacy results are summarized in Table 40 and Figures 44 and 45.

Table 40: Efficacy Results for Patients with TNBC with PD-L1 Expression CPS ≥10

Endpoint	KEYTRUDA with chemotherapy* n=220	Placebo with chemotherapy* n=103
OS†		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio‡ (95% CI)	0.73 (0.55, 0.95)	
p-Value§	0.0093	
24-month OS rate (95% CI)	48.2 (41.4, 54.6)	34.0 (25.0, 43.1)
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¶,#		
ORR, (95% CI)	53% (46, 60)	40% (30, 50)
Complete response	17%	13%
Partial response	36%	27%
Stable disease	28%	44%
Disease control rate Þ	65%	54%
Response Duration¶,#		
Median in months (95% CI)	19.3 (9.9, 29.8)	7.3 (5.3, 15.8)
% with duration ≥ 6 monthsβ	83%	58%
% with duration ≥12 monthsβ	56%	39%

* Chemotherapy: paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin

† Based on the pre-specified final analysis

‡ Based on Cox regression model with Efron's method of tie handlingwith 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)

§ 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)

¶ Assessed by BICR using RECIST 1.1

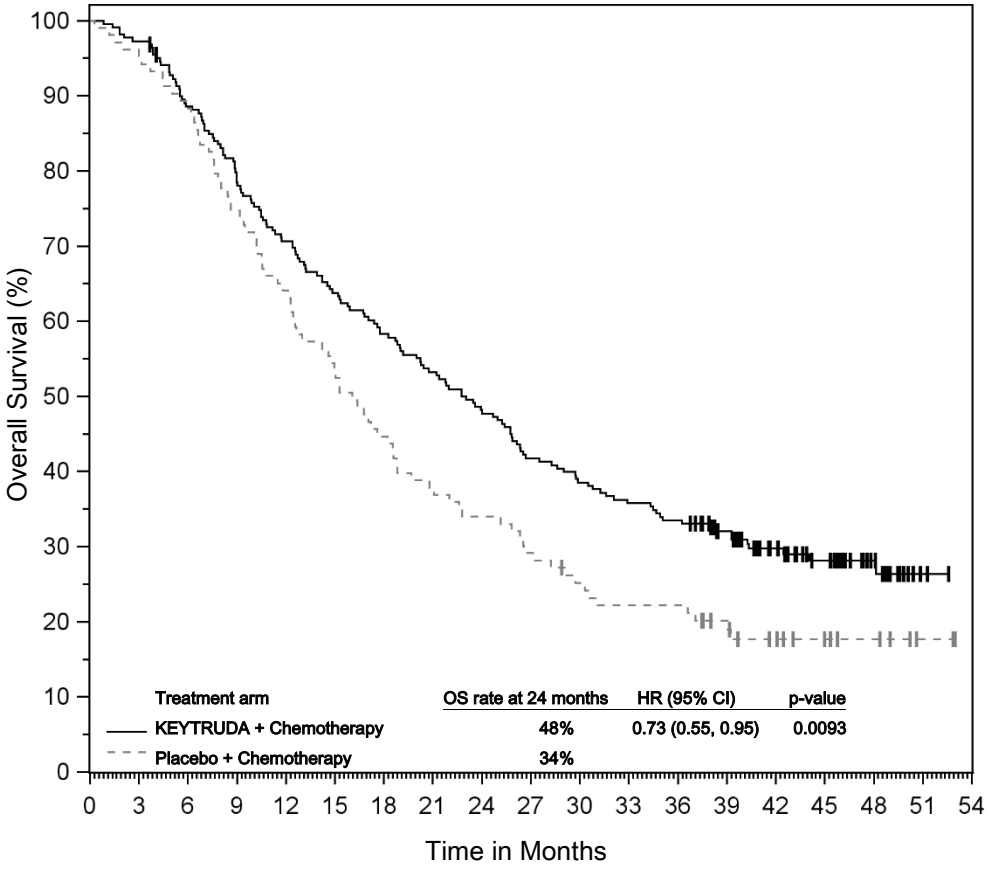
Based on a pre-specified interim analysis

Þ Based on stable disease for at least 24 weeks, or complete response, or partial response

β From product-limit (Kaplan-Meier) method for censored data

At final analysis, the ORR was 53% in the KEYTRUDA with chemotherapy arm and 41% in the placebo with chemotherapy arm. The complete and partial response rates were 17% and 35%, respectively in the KEYTRUDA with chemotherapy arm and 14% and 27%, respectively in the placebo with chemotherapy arm. The median duration of response was 12.8 months (95% CI: 9.9, 25.9) in the KEYTRUDA with chemotherapy arm and 7.3 months (95% CI: 5.5, 15.4) in the placebo with chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 82% and 56% at 6 months and 12 months respectively, in patients in the KEYTRUDA with chemotherapy arm and 60% and 38% at 6 months and 12 months, respectively in patients in the placebo with chemotherapy arm.

Figure 44: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)*

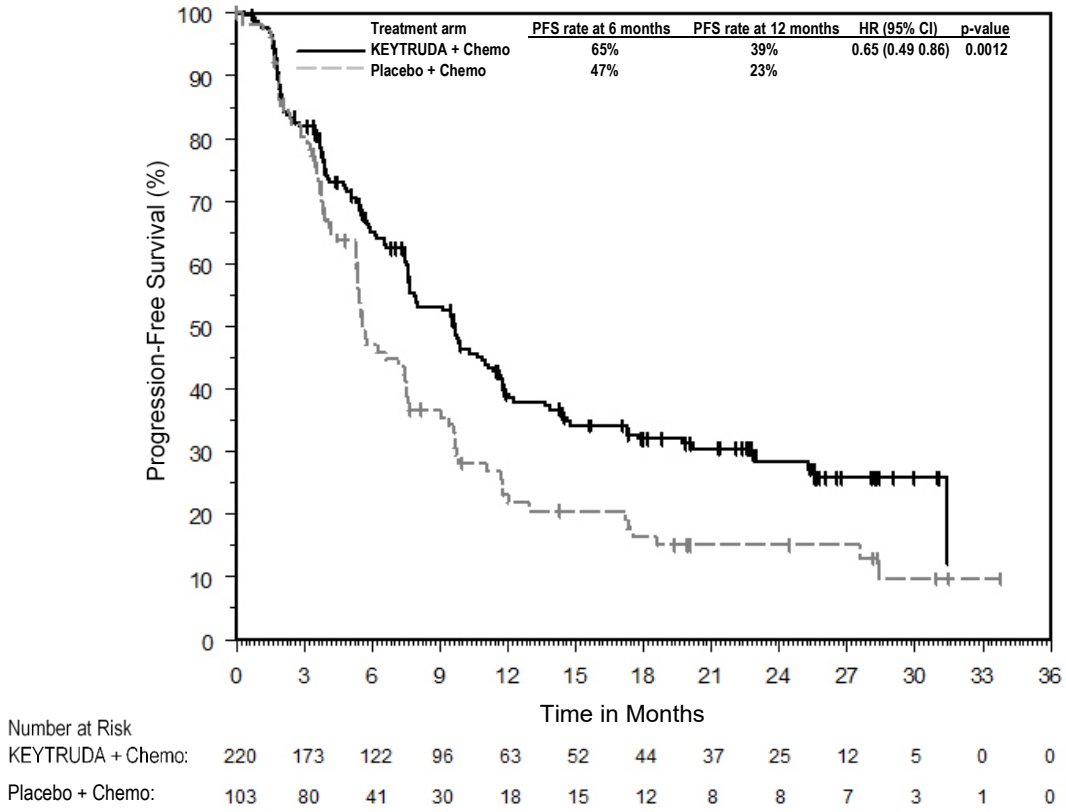


Number at Risk

KEYTRUDA + Chemotherapy	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo + Chemotherapy	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

*Based on the pre-specified final analysis

Figure 45: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)*



*Based on a pre-specified interim analysis

Table 41: Table of subgroup analysis results by chemotherapy combination in CPS ≥10*

	Pembrolizumab with Paclitaxel	Placebo with Paclitaxel	Pembrolizumab with Nab-Paclitaxel†	Placebo with Nab-Paclitaxel	Pembrolizumab with Gemcitabine/ Carboplatin	Placebo with Gemcitabine/ Carboplatin
PFS Hazard Ratio (95% CI)	0.33 (0.14, 0.76)		0.57 (0.34, 0.95)		0.77 (0.53, 1.11)	
Median PFS (months)	9.6	3.6	9.9	5.5	8.0	7.2

* These results were based on an exploratory subgroup analysis and therefore should be interpreted with caution.

† Nab-paclitaxel is currently not available

The impact of the addition of KEYTRUDA to chemotherapy on patient-reported outcomes were assessed using the EORTC QLQ-C30, EORTC QLQ-BR23 and EuroQol EQ-5D. Results from each measure showed that the addition of KEYTRUDA to chemotherapy did not result in a decrease in health-related quality of life through 15 weeks of follow-up.

Cervical Cancer

KEYNOTE-A18: Controlled trial of combination therapy with chemoradiotherapy in patients with high-risk, locally advanced cervical cancer

The efficacy of KEYTRUDA in combination with cisplatin and external beam radiation therapy (EBRT) followed by brachytherapy (BT) was investigated in KEYNOTE-A18, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1060 patients with high-risk, locally advanced cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 601 patients with FIGO (International Federation of Gynecology and Obstetrics) 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 459 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. 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 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. Stage III-IVA), and planned total radiotherapy dose ([EBRT + BT 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. Treatment 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 12 weeks for the first two years, every 24 weeks in year 3, and then annually.

Among the 601 patients with FIGO 2014 Stage III-IVA disease enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 51 years (range: 22 to 87); 16% age 65 or older, 36% White, 1% Black, 34% Asian; 38% Hispanic or Latino; 68% ECOG PS 0 and 32% ECOG PS 1; 93% with CPS ≥1; 71% had positive pelvic and/or positive para aortic lymph node(s), 29% had neither positive pelvic nor para-aortic lymph node, 86% IMRT or VMAT EBRT, 90% ≥70 Gy (EQD2). Eighty-four percent had squamous cell carcinoma and 16% had non squamous histology.

The primary efficacy outcomes were PFS as assessed by investigator according to RECIST v1.1, or histopathologic confirmation, and OS. The trial demonstrated statistically significant improvements in PFS [0.70 (95% CI 0.55, 0.89; p-Value 0.0020)] from the first pre-specified interim analysis and OS [0.67 (95% CI 0.50, 0.90; p-Value 0.0040)] from the second pre-specified interim analysis in the overall population for patients randomized to KEYTRUDA with CRT compared to placebo with CRT. Table 42 summarizes key efficacy measures from the second pre-specified interim analysis in patients with FIGO 2014 Stage III-IVA disease with a median follow-up time of 26.6 months (range: 0.9 to 41.7 months). The Kaplan-Meier curves in patients with FIGO 2014 Stage III-IVA disease for OS and PFS based on this analysis are shown in Figures 46 and 47, respectively.

Table 42: Efficacy Results in KEYNOTE-A18 for Patients with FIGO 2014 Stage III-IVA Cervical Cancer

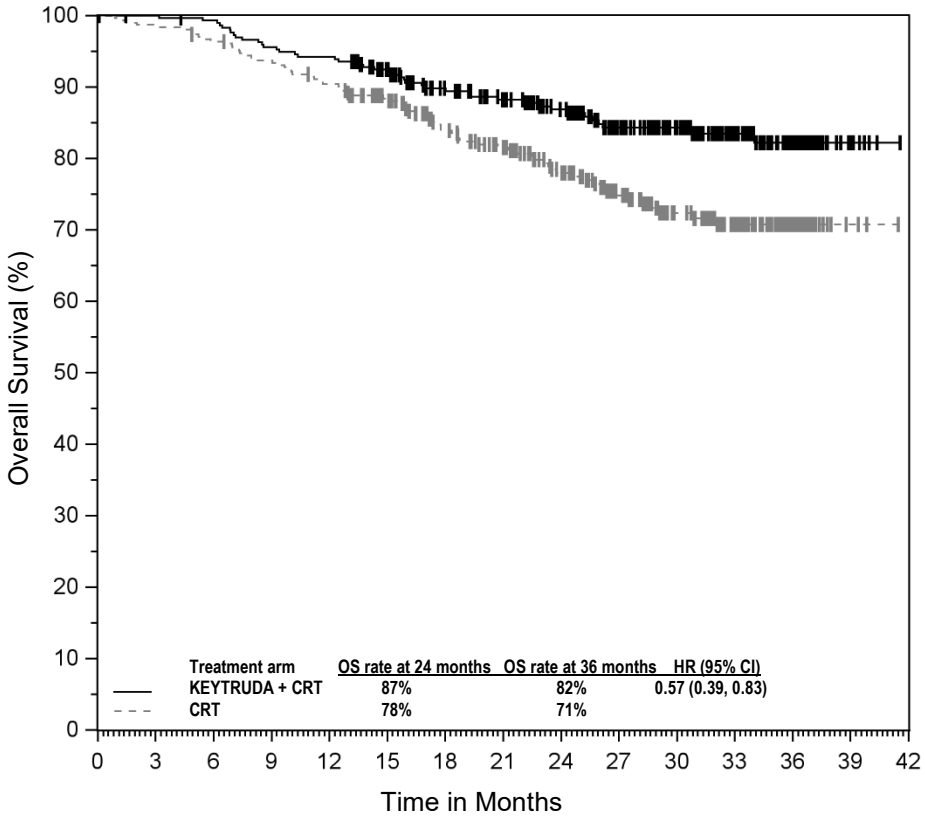
Endpoint	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=296	Placebo with CRT n=305
OS		
Number of patients with event (%)	43 (15%)	73 (24%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.57 (0.39, 0.83)	
PFS by Investigator		
Number of patients with event (%)	79 (27%)	125 (41%)
Median in months (95% CI)	NR (NR, NR)	NR (26.3, NR)
Hazard ratio* (95% CI)	0.57 (0.43, 0.76)	

* Based on the unstratified Cox proportional hazard model

CRT = Chemoradiotherapy

NR = Not reached

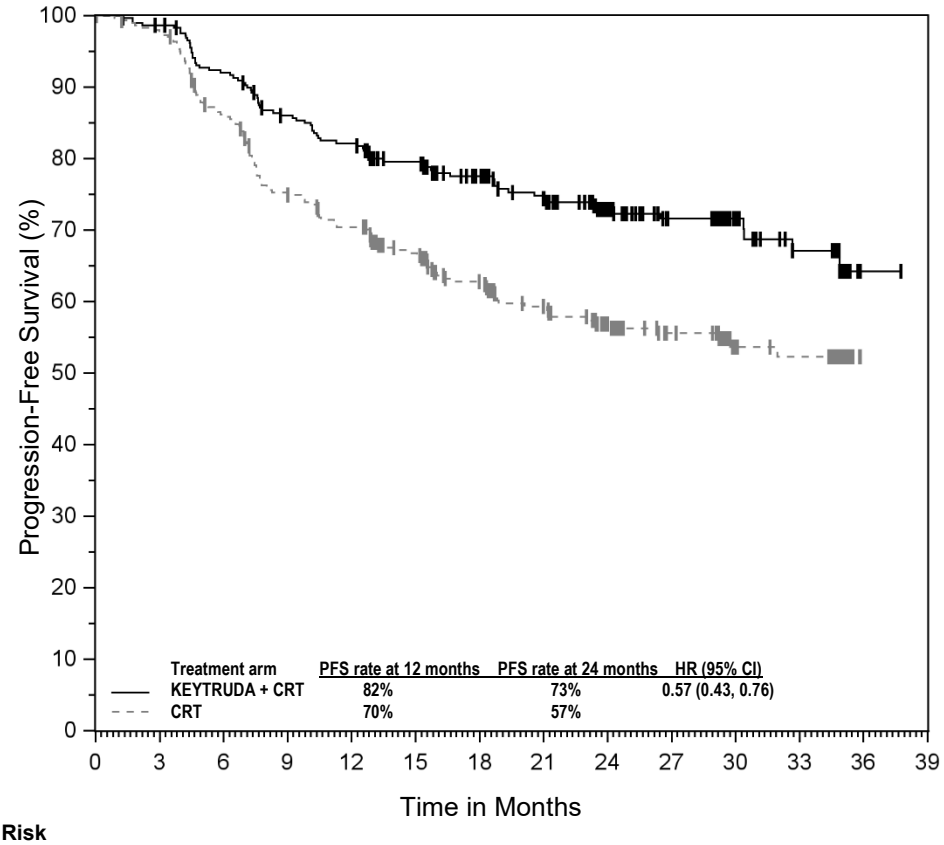
Figure 46: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-A18 for Patients with FIGO 2014 Stage III-IVA Cervical Cancer



Number at Risk

KEYTRUDA + CRT	296	294	291	280	276	254	227	207	184	149	115	77	38	7	0
CRT	305	301	293	284	273	250	216	196	167	134	100	66	28	3	0

Figure 47: Kaplan-Meier Curve for Progression Free Survival by Treatment Arm in KEYNOTE-A18 for Patients with FIGO 2014 Stage III-IVA Cervical Cancer



KEYNOTE-826: Controlled trial of combination therapy in patients with 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, 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
- Treatment Group 2: Placebo plus chemotherapy

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. The option to use bevacizumab was by investigator choice prior to randomization. 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 at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter. 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 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. 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 study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab at a pre-specified interim analysis in the overall population. The median follow-up time was 17.2 months (range: 0.3 to 29.4 months).

Efficacy results are summarized in Table 43, Figure 48, and Figure 49.

Table 43: Efficacy Results for 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 rate	26%	15%
Partial response rate	43%	36%

Duration of response		
Median in months (range)	19.2 (1.3+, 40.9+)	10.4 (1.5+, 40.7+)
% of patients with duration ≥ 12 months#	56	45
% of patients with duration ≥ 24 months#	48	30

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

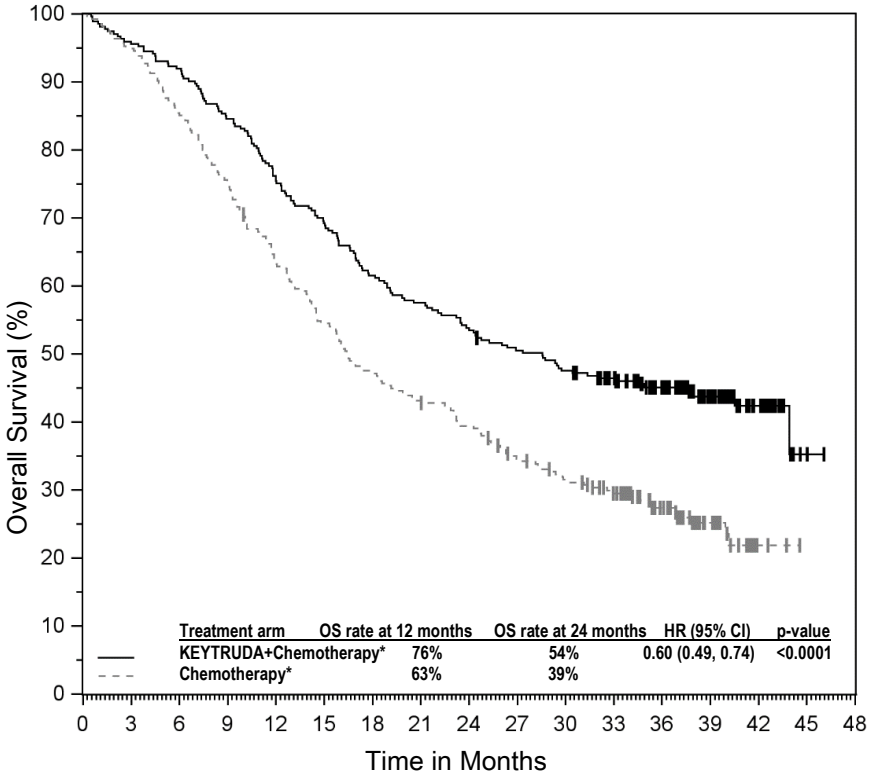
† Based on the stratified Cox proportional hazard model

‡ 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 48: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 in patients with PD-L1 expression (CPS ≥ 1)

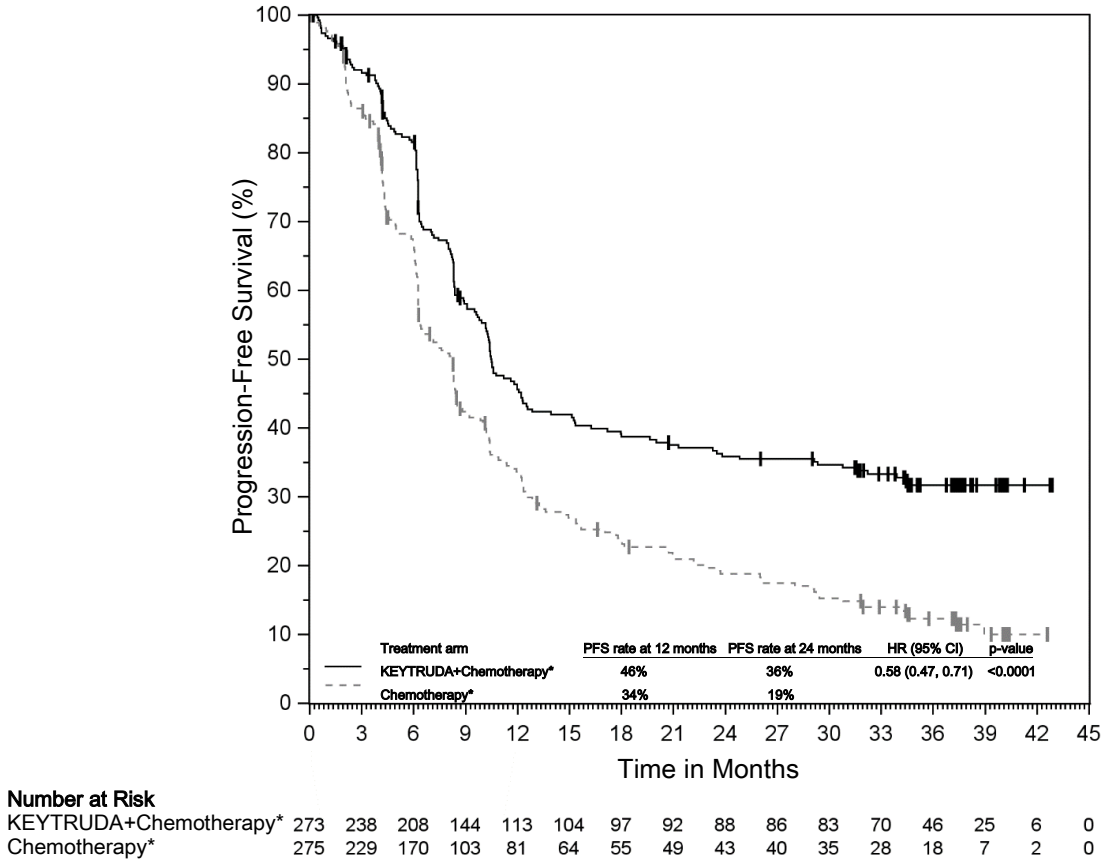


Number at Risk

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

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Figure 49: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-826 in patients with PD-L1 expression (CPS ≥ 1)



* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Patient-reported outcomes (PROs) were assessed using EQ-5D-5L. A prolonged time to deterioration in EQ-5D-5L was observed for patients treated with pembrolizumab plus chemotherapy compared to placebo plus chemotherapy (HR 0.75; 95% CI 0.58-0.97). Over 30 weeks of follow-up, more patients treated with pembrolizumab plus chemotherapy had improved or stable health status/QoL (78.3% vs. 71.1%).

Hepatocellular Carcinoma

KEYNOTE-394: Controlled trial in patients with HCC, previously treated with sorafenib, an anti-angiogenic TKI or oxaliplatin-based chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-394, a multicenter, randomized, placebo-controlled, double-blind trial in 453 patients with HCC, who were previously treated with sorafenib or oxaliplatin-based chemotherapy. 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 prior treatment: sorafenib vs. oxaliplatin-based chemotherapy, macrovascular invasion, etiology (HBV vs. others (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. 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 6 weeks. The primary efficacy outcome measure was OS and the secondary efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using RECIST v1.1.

The study population characteristics were: median age of 54 years (range: 22 to 82), 22% age 65 or older; 85% male; 100% Asian; 41% ECOG PS of 0 and 59% ECOG PS of 1; 100% Child-Pugh Class A; 80% of patients were hepatitis B active positive, 1.3% were hepatitis C active positive, and 0.4% had HBV/HCV co-infection; 91% received prior sorafenib and 9% received prior oxaliplatin-based chemotherapy. Patient characteristics also included extrahepatic disease (78%); macrovascular invasion (11%), BCLC stage C (93%) and B (7%), and baseline AFP ≥200 ng/mL (55%).

Efficacy results are summarized in Table 44 and Figures 50 and 51.

Table 44: Efficacy Results in Patients with Hepatocellular Carcinoma in KEYNOTE-394

Endpoint	KEYTRUDA 200 mg every 3 weeks n=300	Placebo n=153
OS*		

Number (%) of patients with event	222 (74)	128 (84)
Median in months (95% CI)	14.6 (12.6, 18)	13 (10.5, 15.1)
Hazard ratio† (95% CI)	0.79 (0.63, 0.99)	
p-Value‡	0.0180	
PFS§		
Number (%) of patients with event	237 (79)	134 (88)
Median in months (95% CI)	2.6 (1.5, 2.8)	2.3 (1.4, 2.8)
Hazard ratio† (95% CI)	0.74 (0.60, 0.92)	
p-Value‡	0.0032	
Objective Response Rate§		
ORR¶ (95% CI)	13% (9, 17)	1.3% (0.2, 4.6)
Number (%) of complete responses	6 (2)	1 (0.7)
Number (%) of partial responses	32 (11)	1 (0.7)
p-Value#	0.00004	
Response Duration*	n=41	n=2
Median in months Þ (range)	23.9 (2.6+, 44.4+)	5.6 (3.0+, 5.6)
% with duration ≥12 months Þ	65%	0%
% with duration ≥ 24 months Þ	48	0

* 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

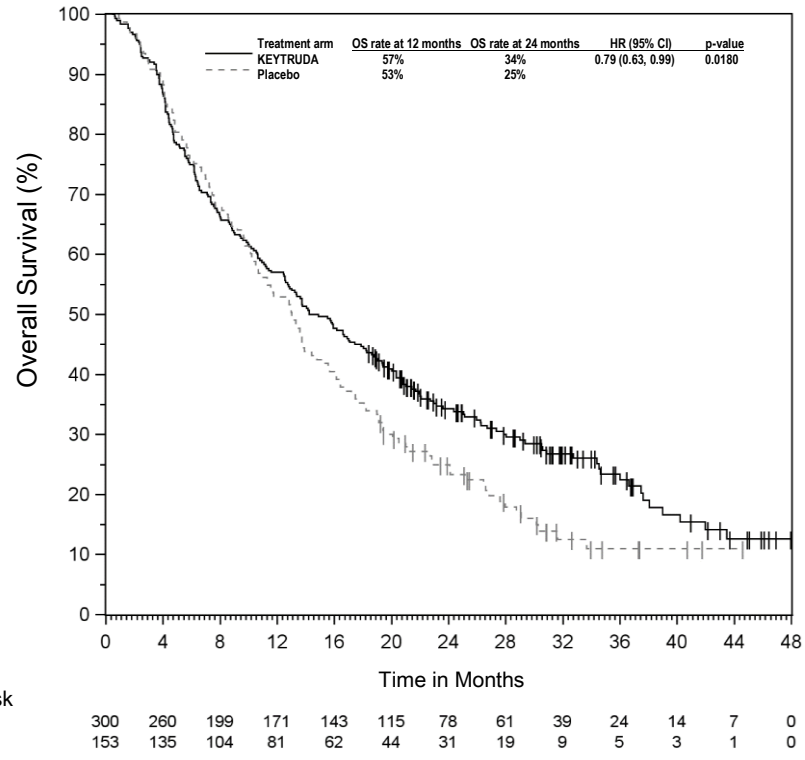
§ Results at pre-specified interim OS analysis

¶ Confirmed complete response or partial response

One-sided p-Value based on the stratified Miettinen and Nurminen analysis

Þ Based on Kaplan-Meier estimation

Figure 50: Kaplan-Meier Curve for Overall Survival in KEYNOTE-394*

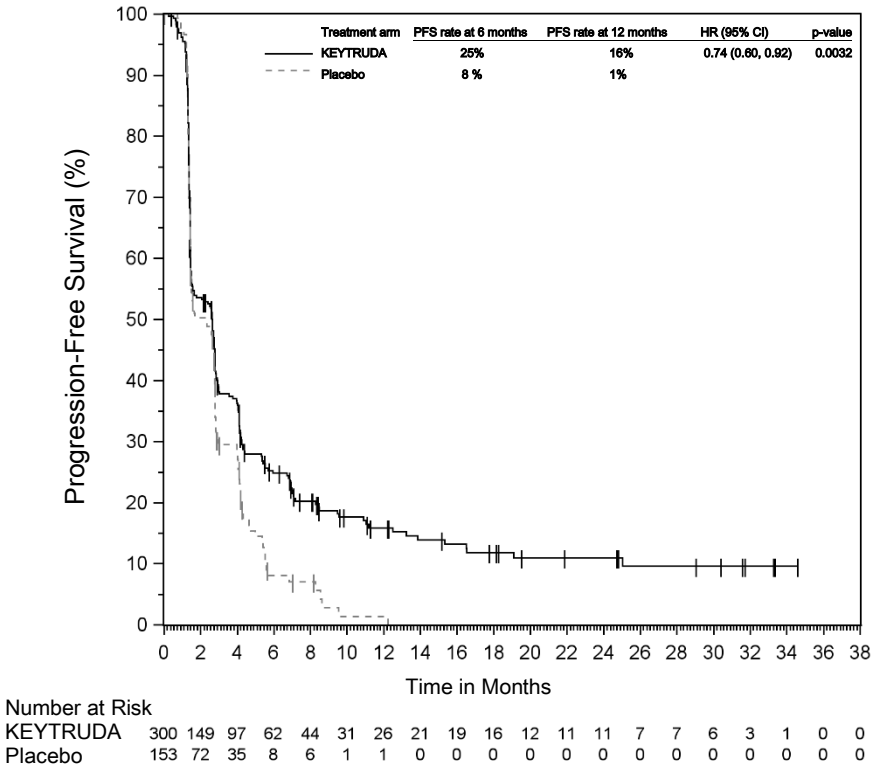


Number at Risk

KEYTRUDA	300	260	199	171	143	115	78	61	39	24	14	7	0
Placebo	153	135	104	81	62	44	31	19	9	5	3	1	0

*Based on the pre-specified final OS analysis

Figure 51: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-394*



*Based on the pre-specified OS interim analysis data cut-off

Pre-specified exploratory analysis of patient-reported outcome (PRO) endpoints using the EORTC QLQ-C30 indicated a smaller decline in global health status/quality of life (GHS/QoL) score from baseline to Week 12 for patients treated with KEYTRUDA compared to placebo (difference in Least Square (LS) means =4.43; 95% CI: 0.47, 8.40). Time to deterioration in the GHS/QoL score was similar for patients treated with KEYTRUDA compared to placebo (HR 0.85; 95% CI: 0.58, 1.25).

Endometrial Carcinoma

KEYNOTE-775: Controlled trial of combination therapy in advanced endometrial carcinoma patients previously treated with systemic therapy

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in a multicenter, randomized, active-controlled, open-label trial, KEYNOTE-775, conducted in 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. The trial excluded patients with endometrial

sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression. Randomization was stratified by MMR status (dMMR or pMMR [not dMMR]). The pMMR stratum was further 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 1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST 1.1-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.

A total of 827 patients were enrolled and randomized to KEYTRUDA in combination with lenvatinib (n=411) or investigator's choice of doxorubicin (n=306) or paclitaxel (n=110). Baseline characteristics 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 tumor 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 endometrial carcinoma: 69% had one, 28% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

The primary efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST 1.1. Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. The median follow-up time for this trial was 11.4 months (range: 0.3 to 26.9 months). Pre-specified interim analysis efficacy measures are summarized in Table 45. Improvements in OS, PFS, and ORR were consistently demonstrated across pre-specified subgroups, including histology, prior therapies, MMR status, and ECOG performance status.

Table 45: Efficacy Results in Patients with Advanced Endometrial Carcinoma in KEYNOTE-775

Endpoint	KEYTRUDA 200 mg every 3 weeks + lenvatinib n=411	Doxorubicin or paclitaxel n=416
OS		
Number (%) of patients with event	188 (46%)	245 (59%)
Median in months (95% CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)
Hazard ratio* (95% CI)	0.62 (0.51, 0.75)	
p-Value†	<0.0001	
PFS		
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		
ORR‡ (95% CI)	32% (27, 37)	15% (11, 18)
p-Value§	<0.0001	
Complete response	7%	3%
Partial response	25%	12%
Stable disease	47%	40%
Disease control rate¶	72%	47%
Response Duration#	n=131	n=61
Median in months (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)
% with duration ≥6 months	72%	43%

% with duration ≥12 months	51%	35%

* 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 MMR Status, ECOG performance status, geographic region, and history of pelvic radiation

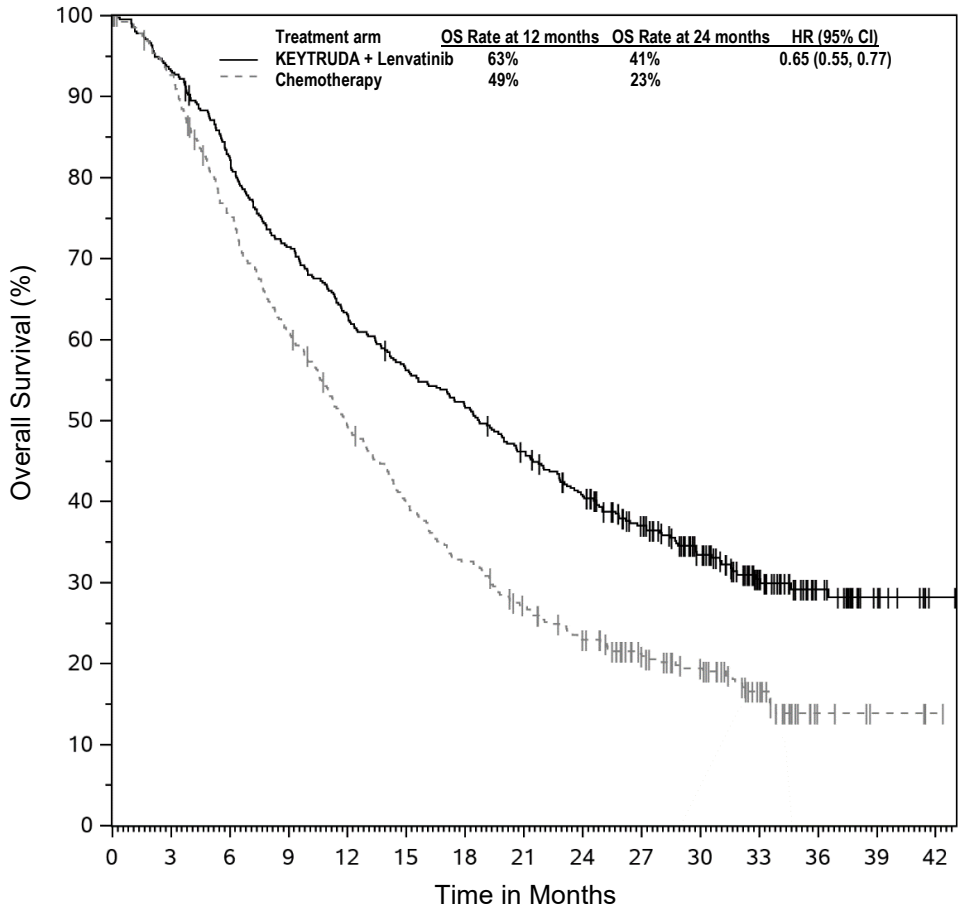
¶ Based on best response of stable disease or better

\# Based on Kaplan-Meier estimation

At the protocol-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]) there were 276 patient events for KEYTRUDA in combination with lenvatinib and 329 patient events for doxorubicin or paclitaxel. Median OS was 18.7 months (95% CI: 15.6, 21.3) for KEYTRUDA in combination with lenvatinib and 11.9 months (95% CI: 10.7, 13.3) for doxorubicin or paclitaxel. The OS HR was 0.65 (95% CI: 0.55, 0.77; nominal p<0.0001). At the time of the protocol-specified final OS analysis, an updated PFS analysis was performed with 320 patient events for KEYTRUDA in combination with lenvatinib and 298 patient events for doxorubicin or paclitaxel. The median PFS was 7.3 months (95% CI: 5.7, 7.6) for KEYTRUDA in combination with lenvatinib and 3.8 months (95% CI: 3.6, 4.2) for doxorubicin or paclitaxel. The PFS HR was 0.56 (95% CI: 0.48, 0.66, nominal p<0.0001). See Figures 52 and 53.

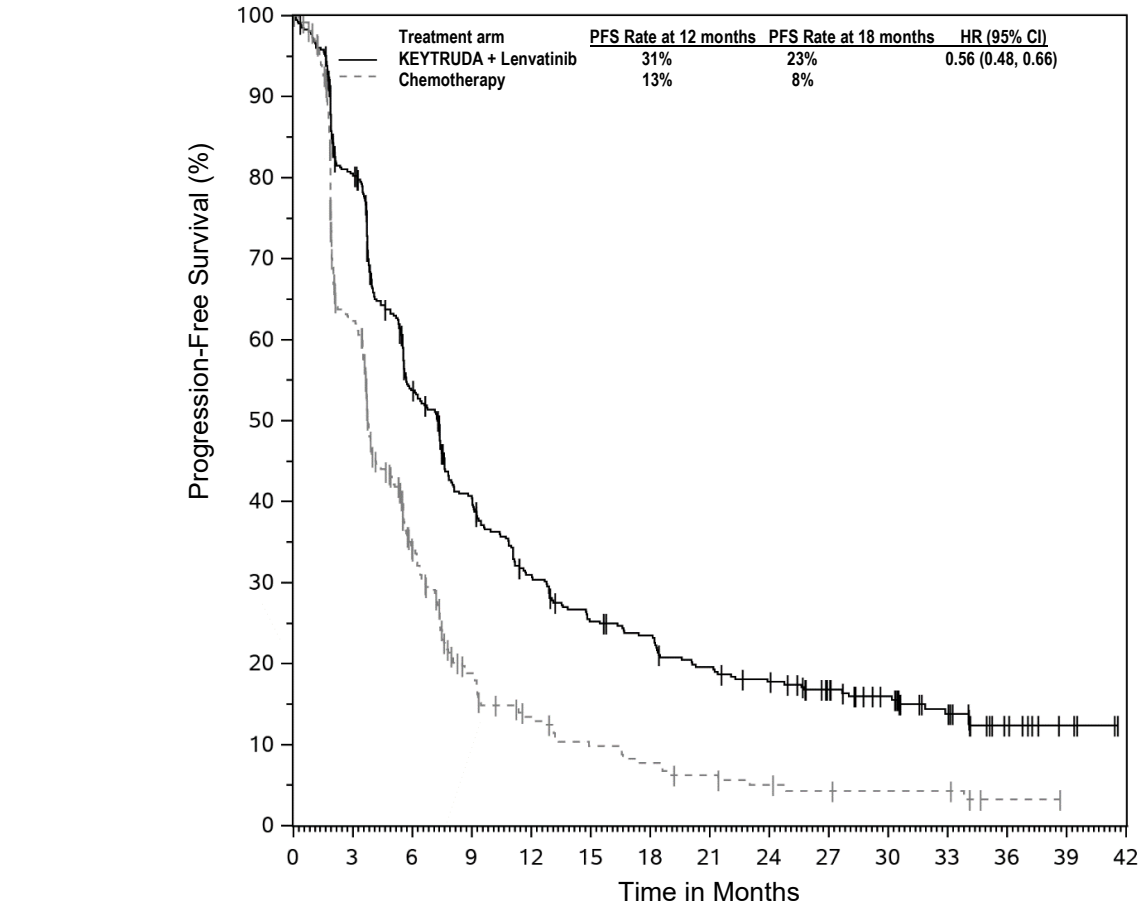
At the time of the protocol-specified final OS analysis, an updated ORR analysis demonstrated ORR of 34% for KEYTRUDA in combination with lenvatinib and 15% for doxorubicin or paclitaxel. The median duration of response was 12.9 months (range: 1.6+, 39.5+) for KEYTRUDA in combination with lenvatinib and 5.7 months (range: 0.0+, 37.1+) for doxorubicin or paclitaxel. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 52% at 12 months, in patients who received KEYTRUDA in combination with lenvatinib, vs. 29% in patients who received doxorubicin or paclitaxel.

Figure 52: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)



Number at Risk															
KEYTRUDA + 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 53: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)



KEYNOTE-868/NRG-GY018: Controlled trial of combination therapy for treatment of patients with primary advanced or recurrent endometrial carcinoma

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868, a multicenter, randomized, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with dMMR and pMMR tumors. Patients had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were 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.

Among the 810 randomized patients, 222 (27%) had dMMR tumor status and 588 (73%) had pMMR tumor status.

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 (24% grade 1, 43% grade 2, 14% grade 3), adenocarcinoma NOS (11%), and other (8% including dedifferentiated/undifferentiated, serous, and mixed epithelial).

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 (17% grade 1, 19% grade 2, 16% grade 3), serous (26%), adenocarcinoma

NOS (10%), clear cell carcinoma (7%), and other (5% including mixed epithelial and dedifferentiated/undifferentiated).

The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. Secondary efficacy outcome measures included OS, ORR, and DoR. The trial demonstrated statistically significant improvements in PFS for patients randomized to KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy in both the dMMR and pMMR populations. The median follow-up time was 13.6 months (range: 0.6 to 39.4 months) and 8.7 months (range: 0.1 to 37.2 months) in the dMMR and pMMR populations, respectively. OS endpoint was not formally assessed within multiplicity control. OS maturity was 12.2% in the dMMR population and 16.8% in the pMMR population. Among the patients who had been randomized to receive placebo in combination with chemotherapy and discontinued from the study, 55% from the dMMR population and 45% from the pMMR population subsequently received post-study therapies that incorporated anti-PD-1/PD-L1 therapy. Table 46 and Figures 54 and 55 summarize the efficacy results for KEYNOTE-868 by MMR status.

Table 46: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	KEYTRUDA with chemotherapy* n=110	Placebo with chemotherapy* n=112	KEYTRUDA with chemotherapy* n=294	Placebo with chemotherapy* n=294
PFS				
Number (%) of patients with event	29 (26%)	60 (54%)	95 (32%)	138 (47%)
Median in months (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.3)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)
Hazard ratio† (95% CI)	0.34 (0.22, 0.53)		0.57 (0.44, 0.74)	
p-Value‡	<0.0001		<0.0001	

OS				
Number (%) of patients with event	10 (9%)	17 (15%)	45 (15%)	54 (18%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)	28.0 (21.4, NR)	27.4 (19.5, NR)
Hazard ratio† (95% CI)	0.55 (0.25, 1.19)		0.79 (0.53, 1.17)	
p-Value§	0.0617		0.1157	

* Chemotherapy (paclitaxel and carboplatin)

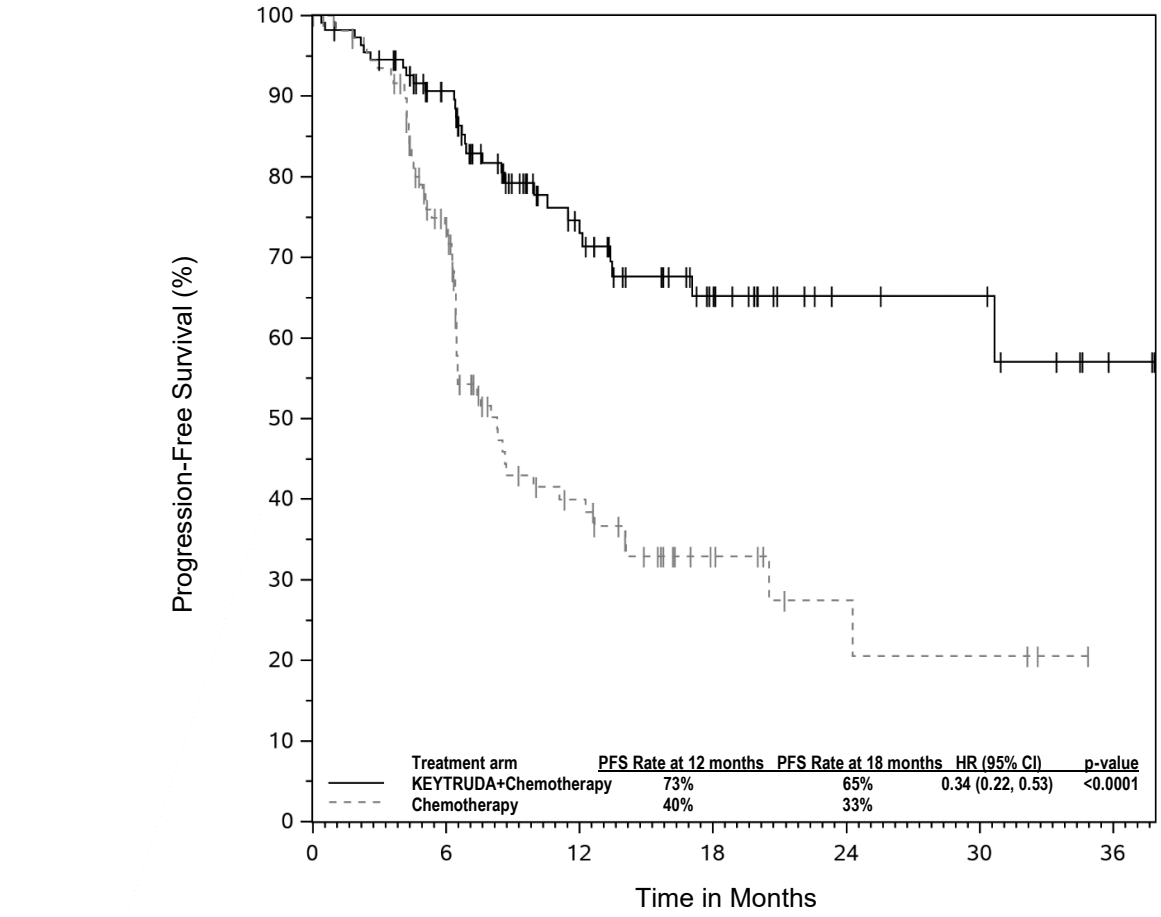
† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00207 for dMMR and 0.00116 for pMMR)

§ Nominal p-Value; no multiplicity adjustment

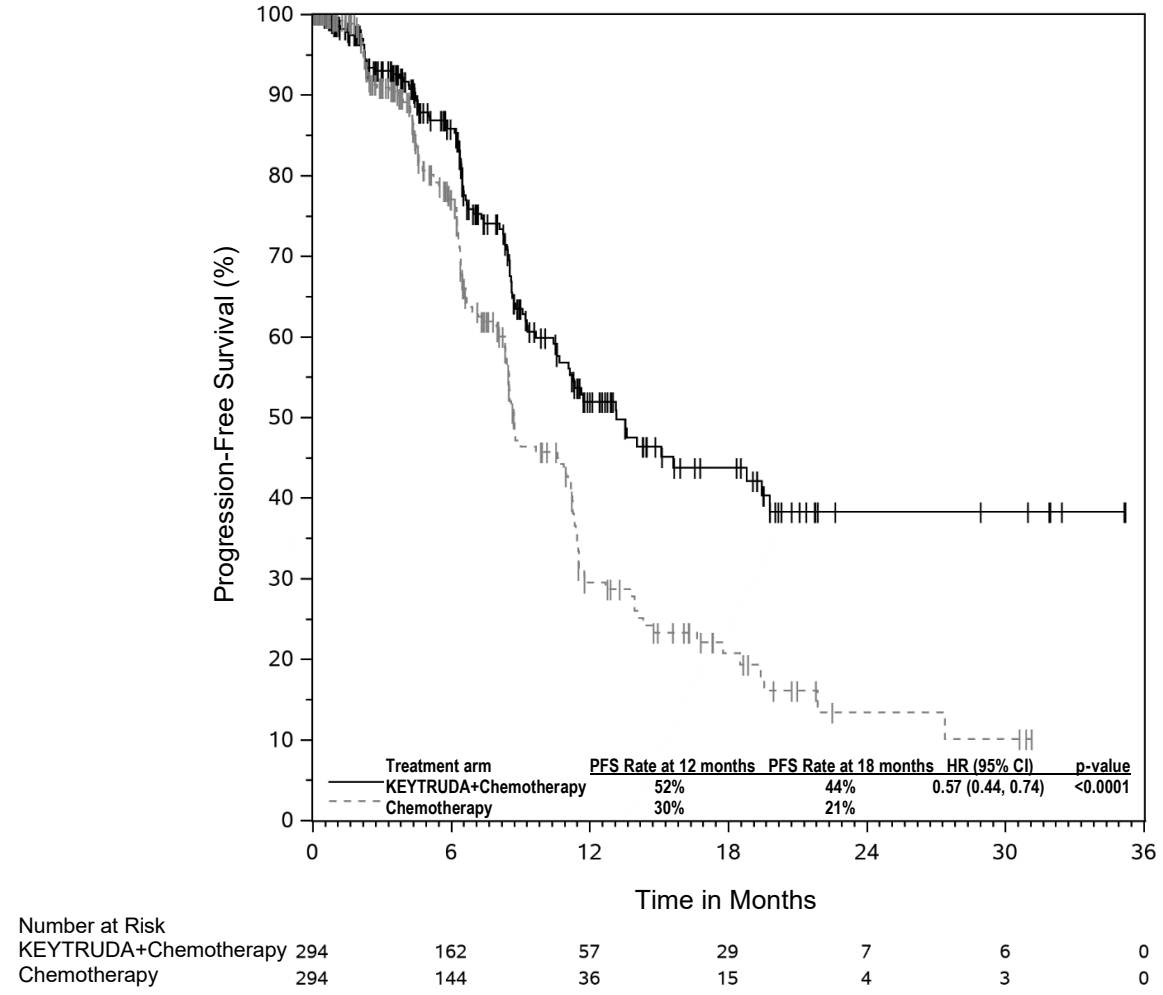
NR=not reached

Figure 54: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



Number at Risk							
KEYTRUDA+Chemotherapy	110	85	45	24	10	9	2
Chemotherapy	112	69	25	9	4	3	0

Figure 55: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



Biliary Tract Carcinoma

KEYNOTE-966: Controlled trial of combination therapy in patients with locally advanced unresectable or metastatic biliary tract carcinoma

The efficacy of KEYTRUDA in combination with gemcitabine and cisplatin was investigated in KEYNOTE-966, 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 vs.

metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomized (1:1) to one of the two treatment groups:

- 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.
- 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

All study medications were administered via intravenous infusion. Treatment is continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment is continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be continued for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 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.

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 according to RECIST v1.1.

Table 47 and Figures 56 and 57 summarize the efficacy results for KEYNOTE-966.

Table 47: Efficacy Results in Patients with BTC 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‡	0.0225	
Objective Response Rate§		
ORR¶ (95% CI)	28.7% (24.9, 32.8)	28.5% (24.8, 32.6)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (26.6%)	146 (27.2%)
p-Value#	0.4735	
Duration of Response*, Þ	n=156	n=152
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%

% with duration ≥24 months	18%	6%

* 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

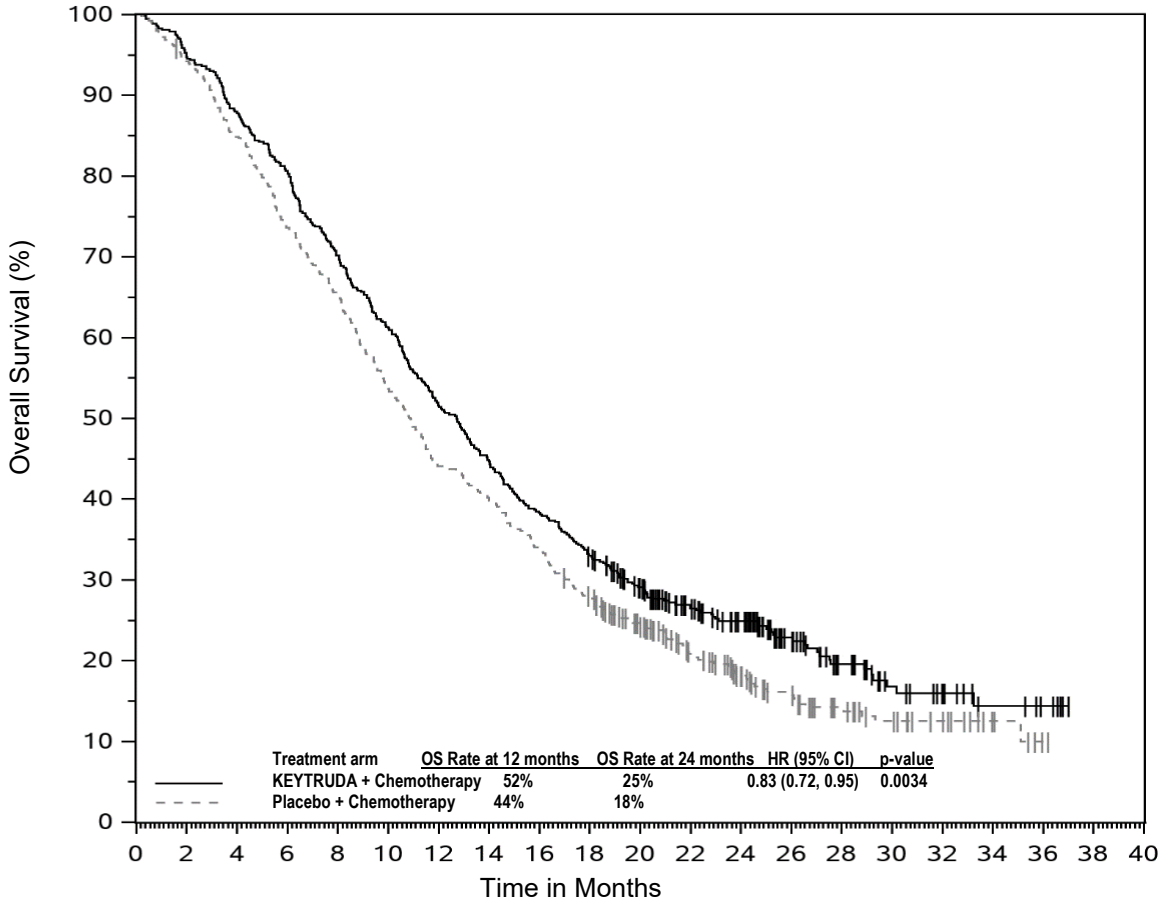
§ Results at pre-specified interim analysis

¶ Confirmed complete response or partial response

One-sided p-Value based on the stratified Miettinen and Nurminen analysis

Þ Based on Kaplan-Meier estimate

Figure 56: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966*

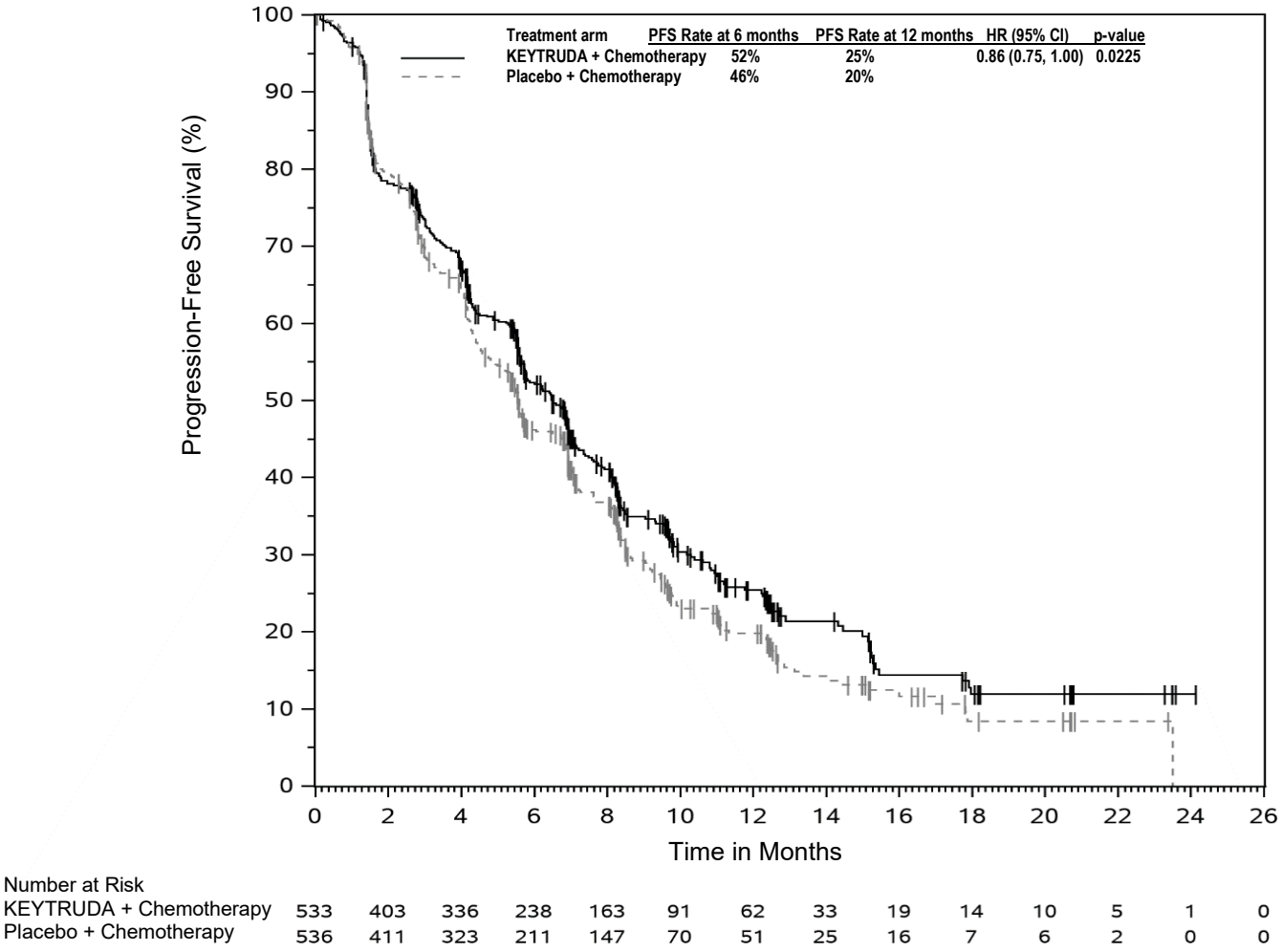


Number at Risk

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

*Based on the pre-specified final OS analysis

Figure 57: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-966*



*Based on the pre-specified interim analysis data cut-off

From baseline to Week 18, pre-specified exploratory patient-reported outcomes (PROs) using the EORTC QLQ-C30 (global health status/quality of life, physical functioning, role functioning), EORTC QLQ-BIL21 (pain and jaundice scores), and EQ-5D-5L visual analog scale (VAS) for patients receiving KEYTRUDA in combination with gemcitabine/cisplatin were similar to those treated with placebo and gemcitabine/cisplatin. From baseline to Week 18, health-related quality of life (HRQoL) was maintained when KEYTRUDA was added to gemcitabine/cisplatin.

Immunogenicity

In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36

(1.8%) of 2034 evaluable patients tested positive for treatment-emergent antibodies against pembrolizumab, of which 9 (0.4%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralizing antibody development.

10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class

KEYTRUDA (pembrolizumab) is an antineoplastic agent, monoclonal antibody.

10.2 Mechanism of Action

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumor cells to inhibit active T-cell immune surveillance. KEYTRUDA is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumor cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

In preclinical murine models, combinations of an anti-mouse PD-1 antibody plus a TKI have demonstrated enhanced anti-tumor activity compared to either agent alone.

10.3 Pharmacodynamics

In peripheral blood of patients who received KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 3 weeks, an increased percentage of activated (i.e., HLA-DR+) CD4+ and CD8+ T-cells was observed after treatment at all doses and schedules without an increase in the circulating T-lymphocyte number.

10.4 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. There are no clinically meaningful differences in pharmacokinetics of pembrolizumab across indications.

Absorption

KEYTRUDA is dosed via the IV 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; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Metabolism

Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its clearance.

Elimination

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life (t½) is 22 days (32%).

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.

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 tumor 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 concentrations with weight-based dosing at 2 mg/kg every

3 weeks in pediatric patients (2 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 analysis in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2) or moderate (GFR <60 and ≥30 mL/min/1.73 m^2) renal impairment compared to patients with normal (GFR ≥90 mL/min/1.73 m^2) 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. KEYTRUDA has not been studied in patients with severe (GFR <30 and ≥15 mL/min/1.73 m^2) renal impairment. *[See Dosage and Administration (2.4).]*

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild and moderate hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN and TB >1.5 to 3 x ULN and any AST, respectively, as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with severe (TB >3 x ULN and any AST) hepatic impairment. *[See Dosage and Administration (2.5).]*

11. ANIMAL TOXICOLOGY

11.1 Chronic Toxicity

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered IV doses of 6, 40 or 200 mg/kg 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, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the

NOAEL and a human dose of 200 mg was 74.

11.2 Carcinogenesis

The carcinogenic potential of pembrolizumab has not been evaluated in long-term animal studies.

11.3 Mutagenesis

The genotoxic potential of pembrolizumab has not been evaluated.

11.4 Reproduction

Animal reproduction studies have not been conducted with KEYTRUDA. The central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining 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. These results indicate a potential risk that administration of KEYTRUDA during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

11.5 Development

Developmental toxicity studies have not been conducted with pembrolizumab. 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.

12. PHARMACEUTICAL FORM

Clear to slightly opalescent, colorless to slightly yellow solution.

13. PHARMACEUTICAL PARTICULARS

13.1 Chemistry

KEYTRUDA (pembrolizumab) is a selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

13.2 Composition

Active Ingredient

Pembrolizumab

Inactive Ingredients (List of excipients)

L-histidine

L-histidine hydrochloride monohydrate

Sucrose

Polysorbate 80

Water for injection

13.3 Storage

Store in a refrigerator (2°C to 8°C; 36°F to 46°F).

Protect from light. Do not freeze. Do not shake.

For storage conditions after dilution of the medicinal product, *see Dosage and Administration (2.1)*.

13.4 Shelf Life

24 months

13.5 Availability

Box, 1 vial @ 4 mL, Reg No. DKI2363501649A1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Registered by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

Distributed by:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

Manufactured by:
MSD International GmbH
T/A MSD Ireland (Carlow)
Dublin Road, Carlow,
Co. Carlow, Ireland

Packed & released by:
Merck Sharp & Dohme B.V., Haarlem,
Netherlands

PI version 60.0
CCDS-MK3475-IV-072025

Anda dapat melaporkan efek samping secara langsung melalui:

DPOC - PT Merck Sharp & Dohme Indonesia Email : dpoc.indonesia@msd.com Fax : +62-21-30078769
Pusat Farmakovigilans c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia Melalui pos: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560 Email: pv-center@pom.go.id Tel : +62-21-4244691 Ext: 1079 Faks : +62-21-42883485 Website: https://e-meso.pom.go.id/

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