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

KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) injection, for subcutaneous use
Initial U.S. Approval: 2025

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

Indications and Usage (1)	07/2026
Dosage and Administration (2)	08/2026
Warnings and Precautions (5)	05/2026

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

KEYTRUDA QLEX is a combination of pembrolizumab, a programmed death receptor-1 (PD-1)-blocking antibody, and berahyaluronidase alfa, an endoglycosidase, indicated:

Melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

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

Malignant Pleural Mesothelioma (MPM)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic MPM. (1.3)

Head and Neck Squamous Cell Cancer (HNSCC)

- for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-authorized test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent. (1.4)
- in combination with platinum and FU for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC. (1.4)
- as a single agent for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-authorized test. (1.4, 2.1)
- as a single agent for the treatment of adult patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. (1.4)

Urothelial Cancer

- in combination with enfortumab vedotin-ejfv, for the treatment of adult patients with locally advanced or metastatic urothelial cancer. (1.5)
- as a single agent for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.5)
- in combination with enfortumab vedotin-ejfv, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment of adult patients with muscle invasive bladder cancer (MIBC). (1.5)
- as a single agent for the treatment of adult patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. (1.5)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-authorized test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. (1.6, 2.1)

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

- for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-authorized test. (1.7, 2.1)

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test. (1.8)
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test. (1.8)

Esophageal Cancer

- for the treatment of adult patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy for patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-authorized test. (1.9, 2.1)

Cervical Cancer

- in combination with chemoradiotherapy, for the treatment of adult patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA). (1.10)
- in combination with chemotherapy, with or without bevacizumab, for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test. (1.10, 2.1)
- as a single agent for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test. (1.10, 2.1)

Hepatocellular Carcinoma (HCC)

- for the treatment of adult patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen. (1.11)

Biliary Tract Cancer (BTC)

- in combination with gemcitabine and cisplatin, for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract cancer. (1.12)

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients 12 years and older with recurrent locally advanced or metastatic Merkel cell carcinoma. (1.13)

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC. (1.14)
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC. (1.14)
- for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. (1.14)
- in combination with belzutifan, for the adjuvant treatment of adult patients with RCC with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. (1.14)

Endometrial Carcinoma

- in combination with carboplatin and paclitaxel, followed by KEYTRUDA QLEX as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma. (1.15)
- in combination with lenvatinib, for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-authorized test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.15, 2.1)
- as a single agent, for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-authorized test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.15, 2.1)

Tumor Mutational Burden-High (TMB-H) Cancer

- for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-authorized test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1] (1.16, 2.1)
- Limitations of Use: The safety and effectiveness of KEYTRUDA QLEX in pediatric patients 12 years and older with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of adult patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation. (1.17)

Triple-Negative Breast Cancer (TNBC)

- for the treatment of adult patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. (1.18)
- in combination with sacituzumab govitecan-hziy, for the first-line treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-authorized test. (1.18, 2.1)
- in combination with chemotherapy, for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-authorized test. (1.18, 2.1)

Ovarian Cancer

- in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of adult patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test, and who have received one or two prior systemic treatment regimens. (1.19, 2.1)

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

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

KEYTRUDA QLEX has different recommended dosage and administration than intravenous pembrolizumab. (2.2)

- KEYTRUDA QLEX is for subcutaneous use in the thigh or abdomen only. (2.2)
- Do not administer KEYTRUDA QLEX intravenously. (2.2)
- KEYTRUDA QLEX must be administered by a healthcare provider. (2.2)

The recommended dose for adults and pediatric patients 12 years and older who weigh greater than 40 kg is:

- Every 3-week dosing (395 mg/4,800 units): Inject 2.4 mL subcutaneously in the abdomen or thigh over 1 minute. (2.3)
- Every 6-week dosing (790 mg/9,600 units): Inject 4.8 mL subcutaneously in the abdomen or thigh over 2 minutes. (2.3)
- For RCC, administer KEYTRUDA QLEX as a single agent in the adjuvant setting, or in the advanced setting with either:
  - axitinib 5 mg orally twice daily or
  - lenvatinib 20 mg orally once daily. (2.3)
- For ccRCC, administer KEYTRUDA QLEX in combination with belzutifan 120 mg orally once daily in the adjuvant setting. (2.3)
- For Endometrial Carcinoma, administer KEYTRUDA QLEX:
  - in combination with carboplatin and paclitaxel regardless of MMR or MSI status, or
  - in combination with lenvatinib 20 mg orally once daily for pMMR or not MSI-H tumors, or
  - as a single agent for MSI-H or dMMR tumors. (2.3)
- See Full Prescribing Information for dosage modifications for adverse reactions and preparation and administration instructions. (2.4, 2.5)

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

Injection: (3)

- 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa per 2.4 mL (165 mg/2,000 units per mL) in a single-dose vial
- 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa per 4.8 mL (165 mg/2,000 units per mL) in a single-dose vial

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

KEYTRUDA QLEX is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients. (4)

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

- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction.
- Hypersensitivity and Administration-Related Reactions: Interrupt injection and resume upon symptom resolution, or permanently discontinue KEYTRUDA QLEX based on the severity of reaction. (5.2)
- Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.4)

- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception. (5.5, 8.1, 8.3)

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

The most common adverse reactions (≥20%) in patients treated with KEYTRUDA QLEX in combination with chemotherapy were nausea, fatigue, and musculoskeletal pain. (6.1)

The safety of KEYTRUDA QLEX for the approved indications is also based on the safety of intravenous pembrolizumab given as a single agent or in combination with other antitumor medicines.

The most common adverse reactions (reported in ≥20% of patients) with intravenous pembrolizumab were:

- As a single agent: fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism. (6.1)
- In combination with chemotherapy or chemoradiotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, hypothyroidism, radiation skin injury, dysphagia, dry mouth and musculoskeletal pain. (6.1)
- In combination with chemotherapy and bevacizumab: peripheral neuropathy, alopecia, anemia, fatigue/asthenia, nausea, neutropenia, diarrhea, hypertension, thrombocytopenia, constipation, arthralgia, vomiting, urinary tract infection, rash, leukopenia, hypothyroidism, decreased appetite, pyrexia, epistaxis, decreased white blood cell count, and stomatitis. (6.1)
- In combination with axitinib: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (6.1)
- In combination with lenvatinib: hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, weight loss, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia, dysphonia, rash, hepatotoxicity, and acute kidney injury. (6.1)
- In combination with belzutifan (reported in ≥25%): decreased hemoglobin, increased alanine aminotransferase, fatigue, increased aspartate aminotransferase, decreased lymphocytes, and increased alkaline phosphatase. (6.1)
- In combination with enfortumab vedotin-ejfv: rash, peripheral neuropathy, fatigue, pruritus, diarrhea, alopecia, weight loss, decreased appetite, dry eye, nausea, constipation, dysgeusia, and urinary tract infection. (6.1)
- In combination with sacituzumab govitecan-hziy: anemia, neutropenia, diarrhea, nausea, fatigue, alopecia, constipation, rash, vomiting, headache and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

KEYTRUDA QLEX™ is indicated for the treatment of adult patients with unresectable or metastatic melanoma.

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

1.2 Non-Small Cell Lung Cancer

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

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

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

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

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

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

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

1.3 Malignant Pleural Mesothelioma

KEYTRUDA QLEX, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

1.4 Head and Neck Squamous Cell Cancer

KEYTRUDA QLEX is indicated for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-authorized test *[see Dosage and Administration (2.1)]*, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

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

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

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

1.5 Urothelial Cancer

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

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

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

KEYTRUDA QLEX, in combination with enfortumab vedotin-ejfv, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment, is indicated for the treatment of adult patients with muscle invasive bladder cancer (MIBC).

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

1.6 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

KEYTRUDA QLEX is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-authorized test, that have progressed following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.

1.7 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

1.8 Gastric Cancer

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

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

1.9 Esophageal Cancer

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

- in combination with platinum- and fluoropyrimidine-based chemotherapy for patients with tumors that express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test *[see Dosage and Administration (2.1)]*, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-authorized test *[see Dosage and Administration (2.1)]*.

1.10 Cervical Cancer

KEYTRUDA QLEX, in combination with chemoradiotherapy (CRT), is indicated for the treatment of adult patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).

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

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

1.11 Hepatocellular Carcinoma

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

1.12 Biliary Tract Cancer

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

1.13 Merkel Cell Carcinoma

KEYTRUDA QLEX is indicated for the treatment of adult and pediatric patients 12 years and older with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

1.14 Renal Cell Carcinoma

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

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

KEYTRUDA QLEX is indicated for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions *[see Clinical Studies (14.16)]*.

KEYTRUDA QLEX, in combination with belzutifan, is indicated for the adjuvant treatment of adult patients with RCC with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

1.15 Endometrial Carcinoma

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

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

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

1.16 Tumor Mutational Burden-High Cancer

KEYTRUDA QLEX is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-authorized test *[see Dosage and Administration (2.1)]*, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.18)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitations of Use: The safety and effectiveness of KEYTRUDA QLEX in pediatric patients 12 years and older with TMB-H central nervous system cancers have not been established.

1.17 Cutaneous Squamous Cell Carcinoma

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

1.18 Triple-Negative Breast Cancer

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

KEYTRUDA QLEX, in combination with sacituzumab govitecan-hziy, is indicated for the first-line treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-authorized test *[see Dosage and Administration (2.1)]*.

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

1.19 Ovarian Cancer

KEYTRUDA QLEX, in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of adult patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test *[see Dosage and Administration (2.1)]*, and who have received one or two prior systemic treatment regimens.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

See information on FDA-authorized tests for intravenous pembrolizumab. Information on FDA-authorized tests for patient selection is available at: http://www.fda.gov/CcompanionDiagnostics.

Patient Selection for Single-Agent Treatment

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

- Stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.4)]*.
- metastatic NSCLC *[see Clinical Studies (14.4)]*.
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.6)]*.
- previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.11)]*.
- recurrent or metastatic cervical cancer with disease progression on or after chemotherapy *[see Clinical Studies (14.12)]*.

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA QLEX as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.8, 14.9)].*

For the TMB-H indication, select patients for treatment with KEYTRUDA QLEX as a single agent based on TMB-H status in tumor specimens *[see Clinical Studies (14.18)].*

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

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

Due to discordance between local tests and FDA-authorized tests, confirmation of MSI-H or dMMR status is recommended by an FDA-authorized test in patients with MSI-H or dMMR solid tumors, if feasible. If unable to perform confirmatory MSI-H/dMMR testing, the presence of TMB ≥10 mut/Mb, as determined by an FDA-authorized test, may be used to select patients for treatment *[see Clinical Studies (14.8)]*.

Patient Selection for Combination Therapy

For use of KEYTRUDA QLEX as a single agent as neoadjuvant treatment, then in combination with radiotherapy (RT) with or without chemotherapy then continued as a single agent as adjuvant treatment, select patients based on presence of positive PD-L1 expression (CPS ≥1) in resectable locally advanced HNSCC *[see Clinical Studies (14.6)].*

For use of KEYTRUDA QLEX in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression (CPS ≥1) in locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, and esophageal or gastroesophageal junction (GEJ) carcinoma *[see Clinical Studies (14.10), (14.11)].*

For use of KEYTRUDA QLEX in combination with chemotherapy, with or without bevacizumab, select patients based on the presence of positive PD-L1 expression in persistent, recurrent, or metastatic cervical cancer *[see Clinical Studies (14.12)].*

For the pMMR/not MSI-H advanced endometrial carcinoma indication, select patients for treatment with KEYTRUDA QLEX in combination with lenvatinib based on MMR or MSI status in tumor specimens *[see Clinical Studies (14.17)]*.

For use of KEYTRUDA QLEX in combination with sacituzumab govitecan-hziy, select patients based on the presence of positive PD-L1 expression in unresectable locally advanced or metastatic TNBC *[see Clinical Studies (14.20)]*.

For use of KEYTRUDA QLEX in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression in locally recurrent unresectable or metastatic TNBC *[see Clinical Studies (14.20)]*.

For use of KEYTRUDA QLEX in combination with paclitaxel, with or without bevacizumab, select patients based on the presence of positive PD-L1 expression (CPS ≥1) in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma *[see Clinical Studies (14.21)]*.

2.2 Important Dosage and Administration Information

- KEYTRUDA QLEX has different recommended dosage and administration instructions than intravenous pembrolizumab.
  - To reduce the risk of medication errors, check the vial labels to ensure that the drug being prepared and administered is KEYTRUDA QLEX for subcutaneous use and not intravenous pembrolizumab.
  - Do not substitute KEYTRUDA QLEX with intravenous pembrolizumab because they have different recommended dosages and routes of administration.
  - Patients receiving intravenous pembrolizumab can switch to subcutaneous KEYTRUDA QLEX at their next scheduled dose.
  - Patients receiving subcutaneous KEYTRUDA QLEX can switch to intravenous pembrolizumab at their next scheduled dose.

- Administer KEYTRUDA QLEX as a subcutaneous injection into the thigh or abdomen, avoiding the 5 cm area around the navel.
- Every 3-week dosing (395 mg/4,800 units): inject 2.4 mL subcutaneously over 1 minute. Treatment duration is provided in Recommended Dosage (Table 1).
- Every 6-week dosing (790 mg/9,600 units): inject 4.8 mL subcutaneously over 2 minutes. Treatment duration is provided in Recommended Dosage (Table 1).
- Inject into healthy skin and never into areas where the skin is red, bruised, tender, or hard.
- Ensure the injection site is at least 2.5 cm from the previous injection site.
- During treatment with KEYTRUDA QLEX, do not administer other medications for subcutaneous use at the same site as KEYTRUDA QLEX.
- Do not administer KEYTRUDA QLEX intravenously.
- KEYTRUDA QLEX must be administered by a healthcare provider.

2.3 Recommended Dosage

The recommended dosages of KEYTRUDA QLEX are presented in Table 1.

- Every 3-week dosing (395 mg pembrolizumab and 4,800 units berahyaluronidase alfa): inject 2.4 mL subcutaneously over 1 minute.
- Every 6-week dosing (790 mg pembrolizumab and 9,600 units berahyaluronidase alfa): inject 4.8 mL subcutaneously over 2 minutes.

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA QLEX	Duration/Timing of Treatment
Monotherapy		
Adult patients with unresectable or metastatic melanoma	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, HNSCC, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, MSI-H or dMMR Endometrial Carcinoma, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with high-risk BCG-unresponsive NMIBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients* (12 years and older who weigh greater than 40 kg) with MSI-H or dMMR Cancer, MCC, or TMB-H Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients* (12 years and older who weigh greater than 40 kg) for adjuvant treatment of melanoma	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease recurrence, unacceptable toxicity, or up to 12 months
Combination Therapy†		
Adult patients with resectable NSCLC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA QLEX as a single agent after surgery for 39 weeks or until

Indication	Recommended Dosage of KEYTRUDA QLEX	Duration/Timing of Treatment
		disease recurrence or unacceptable toxicity
Adult patients with NSCLC, MPM, HNSCC, HER2-negative Gastric Cancer, Esophageal Cancer, or BTC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced or metastatic urothelial cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX after enfortumab vedotin-ejfv when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced HNSCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to cisplatin when given on the same day.	Neoadjuvant: • Administer KEYTRUDA QLEX for 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity. Adjuvant: • Administer KEYTRUDA QLEX in combination with RT with or without cisplatin. • Continue KEYTRUDA QLEX as a single agent. Continue KEYTRUDA QLEX until disease recurrence or unacceptable toxicity or up to one year
Adult patients with MIBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX after enfortumab vedotin-ejfv when given on the same day.	Patients who are cisplatin-eligible¶: Neoadjuvant: • Administer KEYTRUDA QLEX 395 mg/4,800 units every 3 weeks for 4 doses or 790 mg/9,600 units every 6 weeks for 2 doses in combination with enfortumab vedotin-ejfv or until disease progression that precludes curative-intent cystectomy or unacceptable toxicity Adjuvant: • Administer KEYTRUDA QLEX 395 mg/4,800 units every 3 weeks for 13 doses or 790 mg/9,600 units every 6 weeks for 7 doses in combination with enfortumab vedotin-ejfv or until disease recurrence or unacceptable toxicity Patients who are cisplatin-ineligible¶: Neoadjuvant: • Administer KEYTRUDA QLEX 395 mg/4,800 units every 3 weeks for 3 doses in combination with enfortumab vedotin or until disease progression that precludes curative-intent cystectomy or unacceptable toxicity. Adjuvant: • Administer KEYTRUDA QLEX 395 mg/4,800 units every 3 weeks

Indication	Recommended Dosage of KEYTRUDA QLEX	Duration/Timing of Treatment
		for 14 doses or 790 mg/9,600 units every 6 weeks for 7 doses in combination with enfortumab vedotin or until disease recurrence or unacceptable toxicity
Adult patients with HER2-positive Gastric Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to trastuzumab and chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with Cervical Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or for KEYTRUDA QLEX, up to 24 months
Adult patients with RCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX in combination with axitinib 5 mg orally twice daily‡ or Administer KEYTRUDA QLEX in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA QLEX, up to 24 months
Adult patients with Endometrial Carcinoma	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to carboplatin and paclitaxel when given on the same day. or Administer KEYTRUDA QLEX in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA QLEX, up to 24 months
Adult patients with high-risk early-stage TNBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 395 mg/4,800 units every 3 weeks or 4 doses of 790 mg/9,600 units every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA QLEX as a single agent for up to 27 weeks (9 doses of 395 mg/4,800 units every 3 weeks or 5 doses of 790 mg/9,600 units every 6 weeks) or until disease recurrence or unacceptable toxicity§
Adult patients with unresectable locally advanced or metastatic TNBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally recurrent unresectable or metastatic TNBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months

Indication	Recommended Dosage of KEYTRUDA QLEX	Duration/Timing of Treatment
	Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day.	
Adult patients with Ovarian Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to paclitaxel with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adjuvant treatment of adult patients with ccRCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX in combination with belzutifan 120 mg orally once daily.	Until disease recurrence, unacceptable toxicity, or up to 12 months

* The recommended dosage for melanoma, MSI-H or dMMR cancer, MCC and TMB-H cancer has not been established in pediatric patients 12 years and older who weigh 40 kg or less *[see Use in Specific Populations (8.4)]*.

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

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

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

¶ Cisplatin ineligibility is defined as meeting at least one of the following criteria: Creatinine clearance of less than 60 mL/min, ECOG PS 2 or higher, Grade 2 or higher hearing loss, NYHA Class III or higher heart failure, or Grade 2 or higher peripheral neuropathy.

2.4 Dosage Modifications

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

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

Table 2: Recommended Dosage Modifications for Adverse Reactions

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

Adverse Reaction	Severity*	Dosage Modification
Hepatitis with tumor involvement of the liver‡	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold†
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Hypersensitivity and Administration-Related Systemic Reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt injection (if not already fully administered). If symptoms resolve, resume injection
	Grade 3 or 4	Permanently discontinue

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

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

‡ If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA QLEX based on recommendations for hepatitis with no liver involvement.

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

The following table represents dosage modifications that are different from those described above for KEYTRUDA QLEX or in the Full Prescribing Information for the drug administered in combination.

Table 3: Recommended Specific Dosage Modifications for Adverse Reactions for KEYTRUDA QLEX in Combination with Axitinib

Treatment	Adverse Reaction	Severity	Dosage Modification
KEYTRUDA QLEX in combination with axitinib	Liver enzyme elevations*	ALT or AST increases to at least 3 times but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both KEYTRUDA QLEX and axitinib until resolution to Grades 0 or 1†
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST ≥10 times ULN	Permanently discontinue both KEYTRUDA QLEX and axitinib

* Consider corticosteroid therapy

† Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal

Recommended Dose Modifications for Adverse Reactions for KEYTRUDA QLEX in Combination with Lenvatinib

When administering KEYTRUDA QLEX in combination with lenvatinib, modify the dosage of one or both drugs. Withhold or discontinue KEYTRUDA QLEX as shown in Table 2. Refer to lenvatinib prescribing information for additional dose modification information.

Recommended Dose Modifications for Adverse Reactions for KEYTRUDA QLEX in Combination with Sacituzumab Govitecan-hziy

Interrupt or discontinue one or both drugs of the combination or reduce the dose of sacituzumab govitecan-hziy to manage adverse reactions as appropriate. Refer to sacituzumab govitecan-hziy prescribing information for additional dose modification information. Withhold or discontinue KEYTRUDA QLEX as shown in Table 2.

2.5 Preparation

KEYTRUDA QLEX is a ready-to-use solution. Do not dilute KEYTRUDA QLEX.

Do not shake.

Preparation of the Syringe

- Remove KEYTRUDA QLEX vial from refrigerated storage [2°C to 8°C (36°F to 46°F)] and allow it to equilibrate to room temperature [20°C to 25°C (68°F to 77°F)] for at least 30 minutes.
- Prior to preparation for administration, if needed, the unpunctured vial may be stored at room temperature for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Use a sterile, polypropylene or polycarbonate syringe and a stainless steel transfer needle (18 to 21 gauge) to withdraw KEYTRUDA QLEX from the vial.
    - Every 3-week dosing (395 mg pembrolizumab/4,800 units berahyaluronidase alfa): withdraw 2.4 mL into the syringe.
    - Every 6-week dosing (790 mg pembrolizumab/9,600 units berahyaluronidase alfa): withdraw 4.8 mL into the syringe.
- To avoid needle clogging, change the needle to a 25 to 30 gauge, ½-inch, stainless steel hypodermic injection needle immediately prior to subcutaneous injection.
- Discard any unused portion left in the vial.

Storage of Prepared Syringe

The product does not contain a preservative and should be used immediately after withdrawing from the vial. If not used immediately, store the syringe containing KEYTRUDA QLEX with the transfer needle and cap in place:

- At room temperature 20°C to 25°C (68°F to 77°F) for up to 8 hours, or
- In the refrigerator at 2°C to 8°C (36°F to 46°F), protected from light for up to 96 hours. The 96-hour period may include up to 8 hours at room temperature.

Discard if storage time exceeds these limits.

If refrigerated, allow the filled syringe to come to room temperature for at least 30 minutes prior to administration.

Do not freeze.

3 DOSAGE FORMS AND STRENGTHS

KEYTRUDA QLEX is a clear to slightly opalescent, colorless to slightly yellow solution provided as:

- Injection: 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa per 2.4 mL (165 mg/2,000 units per mL) in a single-dose vial
- Injection: 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa per 4.8 mL (165 mg/2,000 units per mL) in a single-dose vial

4 CONTRAINDICATIONS

KEYTRUDA QLEX is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA QLEX is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated adverse reactions.

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

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. For patients with TNBC treated with KEYTRUDA QLEX in the neoadjuvant setting, monitor blood cortisol at baseline, prior to surgery, and as clinically indicated. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA QLEX depending on severity *[see Dosage and Administration (2.4)]*. In general, if KEYTRUDA QLEX requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at

least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

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

Immune-Mediated Pneumonitis

KEYTRUDA QLEX can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 5% (13/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including fatal (0.4%), Grade 3 (2%), and Grade 2 (1.2%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving intravenous pembrolizumab, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of intravenous pembrolizumab in 1.3% (36) of patients and withholding of intravenous pembrolizumab in 0.9% (26) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, 23% had recurrence of pneumonitis. Pneumonitis resolved in 59% of the 94 patients.

In a clinical study enrolling 580 adult patients with resected NSCLC (KEYNOTE-091) who received intravenous pembrolizumab as a single agent for adjuvant treatment, pneumonitis occurred in 41 (7%) patients, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of intravenous pembrolizumab in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted intravenous pembrolizumab, 63% discontinued intravenous pembrolizumab, and 71% had resolution.

Immune-Mediated Colitis

KEYTRUDA QLEX can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.2% (3/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.8%), and Grade 2 (0.4%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of intravenous pembrolizumab in 0.5% (15) of patients and withholding of intravenous pembrolizumab in 0.5% (13) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, 23% had recurrence of colitis. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA QLEX can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of intravenous pembrolizumab in 0.2% (6) of patients and withholding of intravenous pembrolizumab in

0.3% (9) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.

In Combination with Axitinib

KEYTRUDA QLEX in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA QLEX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA QLEX and axitinib, and consider administering corticosteroids as needed *[see Dosage and Administration (2.4)]*.

Intravenous Pembrolizumab in Combination with Axitinib

With the combination of intravenous pembrolizumab and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either intravenous pembrolizumab (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥3 times ULN was observed in 1 patient receiving intravenous pembrolizumab, 16 patients receiving axitinib, and 24 patients receiving both intravenous pembrolizumab and axitinib. All patients with a recurrence of ALT ≥3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

KEYTRUDA QLEX can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA QLEX depending on severity *[see Dosage and Administration (2.4)].*

Adrenal insufficiency occurred in 2% (5/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.4%), and Grade 2 (0.8%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of intravenous pembrolizumab in <0.1% (1) of patients and withholding of intravenous pembrolizumab in 0.3% (8) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement.

Hypophysitis

KEYTRUDA QLEX can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA QLEX depending on severity *[see Dosage and Administration (2.4)]*.

Intravenous Pembrolizumab as a Single Agent

Hypophysitis occurred in 0.6% (17/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 94% (16/17) of patients with hypophysitis; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of intravenous pembrolizumab in 0.1% (4) of patients and withholding of intravenous pembrolizumab in 0.3% (7) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement.

Thyroid Disorders

KEYTRUDA QLEX can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA QLEX depending on severity *[see Dosage and Administration (2.4)].*

Thyroiditis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%). Hyperthyroidism occurred in 8% (20/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (3.2%). Hypothyroidism occurred in 14% (35/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (11%).

Intravenous Pembrolizumab as a Single Agent

Thyroiditis occurred in 0.6% (16/2799) of patients receiving intravenous pembrolizumab, including Grade 2 (0.3%). No patients discontinued intravenous pembrolizumab due to thyroiditis. Intravenous pembrolizumab was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving intravenous pembrolizumab, including Grade 3 (0.1%) and Grade 2 (0.8%). Hyperthyroidism led to permanent discontinuation of intravenous pembrolizumab in <0.1% (2) of patients and withholding of intravenous pembrolizumab in 0.3% (7) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement.

The incidence of new or worsening hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving intravenous pembrolizumab as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.2%) hyperthyroidism.

Hypothyroidism occurred in 8% (237/2799) of patients receiving intravenous pembrolizumab, including Grade 3 (0.1%) and Grade 2 (6.2%). Hypothyroidism led to permanent discontinuation of intravenous pembrolizumab in <0.1% (1) of patients and withholding of intravenous pembrolizumab in 0.5% (14) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving intravenous pembrolizumab as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism.

The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving intravenous pembrolizumab as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA QLEX depending on severity *[see Dosage and Administration (2.4)]*.

Type 1 diabetes mellitus occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy.

Intravenous Pembrolizumab as a Single Agent

Type 1 diabetes mellitus occurred in 0.2% (6/2799) of patients receiving intravenous pembrolizumab. Type 1 diabetes mellitus led to permanent discontinuation in <0.1% (1) of patients and withholding of intravenous pembrolizumab in <0.1% (1) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement. All patients with Type 1 diabetes mellitus required long-term insulin therapy.

Immune-Mediated Nephritis with Renal Dysfunction

KEYTRUDA QLEX can cause immune-mediated nephritis.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 89% (8/9) of patients with nephritis. Nephritis led to permanent discontinuation of intravenous pembrolizumab in 0.1% (3) of patients and withholding of intravenous pembrolizumab in 0.1% (3) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, none had recurrence of nephritis. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA QLEX can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue KEYTRUDA QLEX depending on severity *[see Dosage and Administration (2.4)]*.

Immune-mediated dermatologic adverse reactions occurred in 1.6% (4/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 4 (0.8%), and Grade 3 (0.8%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving intravenous pembrolizumab, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 40% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of intravenous pembrolizumab in 0.1% (2) of patients and withholding of intravenous pembrolizumab in 0.6% (16) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, 6% had recurrence of immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

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

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

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

Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis (2.8%), duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica

Endocrine: Hypoparathyroidism

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

Other: Myocarditis-Myositis-Myasthenia Gravis (or Myasthenia-Like) Overlap Syndrome, reporting as the co-occurrence of either two or all three adverse reactions.

5.2 Hypersensitivity and Administration-Related Reactions

KEYTRUDA QLEX can cause severe or life-threatening administration-related reactions, including hypersensitivity and anaphylaxis. In Study MK-3475A-D77, hypersensitivity and administration-related systemic reactions occurred in 3.2% (8/251) of patients receiving KEYTRUDA QLEX, including Grade 2 (2.8%). Monitor patients for signs and symptoms of administration-related systemic reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt injection (if not already fully administered) and resume if symptoms resolve for mild or moderate hypersensitivity and administration-related systemic reactions. For severe or life-threatening hypersensitivity and administration-related systemic reactions, stop injection and permanently discontinue KEYTRUDA QLEX *[see Dosage and Administration (2.4)].*

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Increased Mortality in Patients with Multiple Myeloma when Pembrolizumab is Added to a Thalidomide Analogue and Dexamethasone

In two randomized trials in patients with multiple myeloma, the addition of intravenous pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, KEYTRUDA QLEX can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA QLEX and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.
- Hypersensitivity and Administration-Related Reactions *[see Warnings and Precautions (5.2)].*

6.1 Clinical Trials Experience

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to intravenous pembrolizumab as a single agent in 2799 patients in three randomized, open-label, active-controlled trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA QLEX in combination with platinum doublet chemotherapy in a randomized, open-label, active-controlled trial (Study MK-3475A-D77), which enrolled 251 patients with NSCLC; intravenous pembrolizumab as a single agent in a randomized, placebo-controlled trial (KEYNOTE-091), which enrolled 580 patients with resected NSCLC; a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active-controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE-426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, patients were administered either KEYTRUDA QLEX 790 mg/9,600 units every 6 weeks or intravenous pembrolizumab at doses of 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. Among the 2799 patients who received intravenous pembrolizumab, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The most common adverse reactions (≥20%) in patients who received KEYTRUDA QLEX in combination with chemotherapy were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).

The safety of KEYTRUDA QLEX for the approved indications is also based on the safety of intravenous pembrolizumab given as a single agent or in combination with other antitumor medicines.

The most common adverse reactions (≥20%) in patients who received intravenous pembrolizumab were:

- as a single agent: fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism.
- in combination with chemotherapy or chemoradiotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, hypothyroidism, radiation skin injury, dysphagia, dry mouth, and musculoskeletal pain.
- in combination with chemotherapy and bevacizumab: peripheral neuropathy, alopecia, anemia, fatigue/asthenia, nausea, neutropenia, diarrhea, hypertension, thrombocytopenia, constipation, arthralgia, vomiting, urinary tract infection, rash, leukopenia, hypothyroidism, decreased appetite, pyrexia, epistaxis, decreased white blood cell count, and stomatitis.
- in combination with axitinib: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.
- in combination with lenvatinib: hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, weight loss, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia, dysphonia, rash, hepatotoxicity, and acute kidney injury.
- in combination with belzutifan (reported in ≥25%): decreased hemoglobin, increased alanine aminotransferase, fatigue, increased aspartate aminotransferase, decreased lymphocytes, and increased alkaline phosphatase.
- in combination with enfortumab vedotin-ejfv: rash, peripheral neuropathy, fatigue, pruritus, diarrhea, alopecia, weight loss, decreased appetite, dry eye, nausea, constipation, dysgeusia, and urinary tract infection.
- in combination with sacituzumab govitecan-hziy: anemia, neutropenia, diarrhea, nausea, fatigue, alopecia, constipation, rash, vomiting, headache and abdominal pain.

Adverse Reactions in Patients with NSCLC Treated with KEYTRUDA QLEX

The safety of KEYTRUDA QLEX compared to intravenous pembrolizumab in patients with previously untreated, metastatic NSCLC with no EGFR, ALK or ROS1 genomic tumor aberrations was evaluated in Study MK-3475A-D77 *[see Clinical Studies (14.1)].* A total of 377 patients received either KEYTRUDA QLEX 790 mg/9,600 units every 6 weeks in combination with platinum doublet chemotherapy (n=251) or intravenous pembrolizumab 400 mg every 6 weeks in combination with platinum doublet chemotherapy (n=126).

Among patients who received KEYTRUDA QLEX, 58% were exposed for 6 months or longer and 3.2% were exposed for greater than one year.

The median age of patients who received KEYTRUDA QLEX was 65 years (range: 39 to 87); 73% male, 63% White; 29% Asian, 4.8% multiple races, 2% Black or African American, 0.8% Alaska Native or American Indian; and 29% were of Hispanic or Latino ethnicity.

Serious adverse reactions occurred in 39% of patients who received KEYTRUDA QLEX in combination with chemotherapy. Serious adverse reactions in ≥1% of patients who received KEYTRUDA QLEX were pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%). Fatal adverse reactions occurred in 10% of patients who received KEYTRUDA QLEX in combination with chemotherapy including pneumonia (3.2%), neutropenic sepsis (2%), death not otherwise specified (1.6%), respiratory failure (1.2%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%).

Permanent discontinuation of KEYTRUDA QLEX due to an adverse reaction occurred in 16% of patients. Adverse reactions which resulted in permanent discontinuation of KEYTRUDA QLEX in ≥2% of patients included pneumonia and pneumonitis.

Dosage interruptions of KEYTRUDA QLEX due to an adverse reaction occurred in 45% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia, anemia, thrombocytopenia, pneumonia, rash, and increased aspartate aminotransferase.

Tables 4 and 5 summarize the adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA QLEX in Study MK-3475A-D77.

Table 4: Adverse Reactions Occurring in ≥10% of Patients with Metastatic NSCLC Receiving KEYTRUDA QLEX in Study MK-3475A-D77

Adverse Reaction	KEYTRUDA QLEX and Platinum Doublet Chemotherapy (n=251)		Intravenous Pembrolizumab and Platinum Doublet Chemotherapy (n=126)	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	25	1.2	25	0.8
Diarrhea[†]	16	2	14	0.8
Constipation	14	0	18	1.6
General				
Fatigue[‡]	25	3.6	26	3.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[§]	21	2.4	30	2.4
Skin and Subcutaneous Tissue				
Rash[¶]	18	2	19	0.8
Pruritus	12	0	13	0.8
Endocrine				
Hypothyroidism	14	0	12	0
Infections				
Pneumonia[#]	17	10	16	7
Nervous System				
Peripheral neuropathy[Þ]	11	0.4	14	0
Metabolism and Nutrition				

Decreased appetite	11	0.8	21	2.4
Hyperglycemia	11	0.8	11	0.8
Respiratory, Thoracic and Mediastinal				
Cough [β]	10	0	11	0.8

* Graded per NCI CTCAE V5.0

† Includes diarrhea, colitis, and enterocolitis.

‡ Includes fatigue, asthenia.

§ Includes musculoskeletal pain, arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, non-cardiac chest pain, and pain in extremity.

¶ Includes rash, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, eczema, erythema multiforme, immune-mediated dermatitis, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin exfoliation.

Includes pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung abscess, pneumocystis jirovecii pneumonia, pneumonia bacterial, and pneumonia mycoplasmal.

Þ Includes neuropathy peripheral, hypoaesthesia, neuralgia, paraesthesia, and peripheral sensory neuropathy.

β Includes cough, productive cough, and upper-airway cough syndrome.

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA QLEX included local injection site reactions (2.4%).

Table 5: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Metastatic NSCLC Receiving KEYTRUDA QLEX in Study MK-3475A-D77

Laboratory Test*	KEYTRUDA QLEX and Platinum Doublet Chemotherapy		Intravenous Pembrolizumab and Platinum Doublet Chemotherapy	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Anemia	80	22	86	26
Leukopenia	61	13	52	10
Neutropenia	58	28	49	19
Lymphopenia	55	22	54	18
Thrombocytopenia	43	11	41	6
Chemistry				
Increased AST	43	2.5	38	3.2
Hypoalbuminemia	38	0.4	39	0
Increased ALT	37	2.1	36	0.8
Hyponatremia	35	4.1	42	7
Increased creatinine	33	4.5	38	6
Hypocalcemia	31	2.1	31	2.4
Increased alkaline phosphatase	29	0.4	34	0
Hypokalemia	21	5	24	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA QLEX plus platinum doublet chemotherapy (range: 240 to 246 patients) and intravenous pembrolizumab plus platinum doublet chemotherapy (range: 124 to 125 patients).

† Graded per NCI CTCAE V5.0

Adverse Reactions in Adult and Pediatric Patients Treated with Intravenous Pembrolizumab

The safety of KEYTRUDA QLEX for its approved indications *[see Indications and Usage (1)]* has been established in adequate and well-controlled studies of KEYTRUDA QLEX in combination with platinum doublet chemotherapy (Study MK-3475A-D77) and intravenous pembrolizumab, as a single agent or in combination therapy, across tumor types.

Below is a description of adverse reactions of intravenous pembrolizumab in these adequate and well-controlled studies.

Melanoma

Ipilimumab-Naive Melanoma

The safety of intravenous pembrolizumab for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic

therapy was investigated in KEYNOTE-006. KEYNOTE-006 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received intravenous pembrolizumab 10 mg/kg every 2 weeks (n=278) or intravenous pembrolizumab 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.3)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for intravenous pembrolizumab and similar in both treatment arms. Fifty-one and 46% of patients received intravenous pembrolizumab 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 32% had an elevated lactate dehydrogenase (LDH) value at baseline; 65% had M1c stage disease; 9% with history of brain metastasis; and approximately 36% had been previously treated with systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both intravenous pembrolizumab arms. Adverse reactions leading to permanent discontinuation of intravenous pembrolizumab occurred in 9% of patients. Adverse reactions leading to discontinuation of intravenous pembrolizumab in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). Tables 6 and 7 summarize selected adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-006.

Table 6: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-006

Adverse Reaction	Intravenous Pembrolizumab 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition				
Decreased appetite	16	0.5	14	0.8
Nervous System				
Headache	14	0.2	14	0.8

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving intravenous pembrolizumab were diarrhea (26%), nausea (21%), and pruritus (17%).

Table 7: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving Intravenous Pembrolizumab in KEYNOTE-006

Laboratory Test†	Intravenous Pembrolizumab 10 mg/kg every 2 or 3 weeks		Ipilimumab	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: intravenous pembrolizumab n=429 and ipilimumab n=183; hypercholesterolemia: intravenous pembrolizumab n=484 and ipilimumab n=205.

‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving intravenous pembrolizumab were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2% Grades 3-4).

Ipilimumab-Refractory Melanoma

The safety of intravenous pembrolizumab in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was investigated in KEYNOTE-002. KEYNOTE-002 was a multicenter, partially blinded (intravenous pembrolizumab dose), randomized (1:1:1), active-controlled trial in which 528 patients received intravenous pembrolizumab 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.3)]*. Patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure to intravenous pembrolizumab 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to intravenous pembrolizumab 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). In the intravenous pembrolizumab 2 mg/kg arm, 36% of patients were exposed to intravenous pembrolizumab for ≥6 months and 4% were exposed for ≥12 months. In the 10 mg/kg arm, 41% of patients were exposed to intravenous pembrolizumab for ≥6 months and 6% of patients were exposed to intravenous pembrolizumab for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89); 61% male; 98% White; 41% had an elevated LDH value at baseline; 83% had M1c stage disease; 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor); and 15% with history of brain metastasis.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both intravenous pembrolizumab arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving intravenous pembrolizumab; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 14% of patients; the

most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-002.

Table 8: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-002

Adverse Reaction	Intravenous Pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal				
Cough	18	0	16	0
General				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Musculoskeletal and Connective Tissue				
Arthralgia	14	0.6	10	1.2

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm
† Chemotherapy: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin
‡ Graded per NCI CTCAE v4.0
§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving intravenous pembrolizumab were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 9: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving Intravenous Pembrolizumab in KEYNOTE-002

Laboratory Test†	Intravenous Pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased alkaline phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Decreased bicarbonate	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: intravenous pembrolizumab n=247 and chemotherapy n=116; decreased bicarbonate: intravenous pembrolizumab n=263 and chemotherapy n=123.
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving intravenous pembrolizumab were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

Adjuvant Treatment of Resected Stage IIB or IIC Melanoma

Among the 969 patients with Stage IIB or IIC melanoma enrolled in KEYNOTE-716 *[see Clinical Studies (14.3)]* treated with intravenous pembrolizumab, the median duration of exposure to intravenous pembrolizumab was 9.9 months (range: 0 to 15.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Adverse reactions occurring in patients with Stage IIB or IIC melanoma were similar to those occurring in 1011 patients with Stage III melanoma from KEYNOTE-054 or the 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent.

Adjuvant Treatment of Stage III Resected Melanoma

The safety of intravenous pembrolizumab as a single agent was investigated in KEYNOTE-054, a randomized (1:1) double-blind trial in which 1019 patients with completely resected Stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma received 200 mg of intravenous pembrolizumab by intravenous infusion every 3 weeks (n=509) or placebo (n=502) for up to one year *[see Clinical Studies (14.3)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Seventy-six percent of patients received intravenous pembrolizumab for 6 months or longer.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had Stage IIIA, 46% had Stage IIIB, 18% had Stage IIIC (1-3 positive lymph nodes), and 20% had Stage IIIC (≥4 positive lymph nodes).

Two patients treated with intravenous pembrolizumab died from causes other than disease progression; causes of death were drug reaction with eosinophilia and systemic symptoms and autoimmune myositis with respiratory failure. Serious adverse reactions occurred in 25% of patients receiving intravenous pembrolizumab. Adverse reactions leading to permanent discontinuation occurred in 14% of patients receiving intravenous pembrolizumab; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 19% of patients; the most common (≥1%) were diarrhea (2.4%), pneumonitis (2%), increased ALT (1.4%), arthralgia (1.4%), increased AST (1.4%), dyspnea (1%), and fatigue (1%). Tables 10 and 11 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-054.

Table 10: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-054

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks n=509		Placebo n=502	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	28	1.2	26	1.2
Nausea	17	0.2	15	0
Skin and Subcutaneous Tissue				
Pruritus	19	0	12	0
Rash	13	0.2	9	0
Musculoskeletal and Connective Tissue				
Arthralgia	16	1.2	14	0
Endocrine				
Hypothyroidism	15	0	2.8	0
Hyperthyroidism	10	0.2	1.2	0
Respiratory, Thoracic and Mediastinal				
Cough	14	0	11	0
General				
Asthenia	11	0.2	8	0
Influenza like illness	11	0	8	0
Investigations				
Weight loss	11	0	8	0

* Adverse reactions occurring at same or higher incidence than in placebo arm
† Graded per NCI CTCAE v4.03

Table 11: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving Intravenous Pembrolizumab in KEYNOTE-054

Laboratory Test†	Intravenous Pembrolizumab 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Increased ALT	25	2.4	15	0.2
Increased AST	22	1.8	14	0.4
Hematology				
Lymphopenia	22	1	15	1.2

* Laboratory abnormalities occurring at same or higher incidence than placebo.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 502 to 505 patients) and placebo (range: 491 to 497 patients).
‡ Graded per NCI CTCAE v4.03

NSCLC

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The safety of intravenous pembrolizumab in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.4)]*. A total of 607 patients received intravenous pembrolizumab 200 mg, pemetrexed and platinum every 3 weeks for 4 cycles followed by intravenous pembrolizumab and pemetrexed (n=405) or placebo, pemetrexed, and platinum every 3 weeks for 4 cycles followed by placebo and pemetrexed (n=202). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 7.2 months (range: 1 day to 20.1 months). Sixty percent of patients in the intravenous pembrolizumab arm were

exposed to intravenous pembrolizumab for ≥6 months. Seventy-two percent of patients received carboplatin.

The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 or older; 59% male; 94% White and 3% Asian; and 18% with history of brain metastases at baseline.

Intravenous pembrolizumab was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%). Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-189.

Table 12: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-189

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=405		Placebo Pemetrexed Platinum Chemotherapy n=202	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	3.5	52	3.5
Constipation	35	1.0	32	0.5
Diarrhea	31	5	21	3.0
Vomiting	24	3.7	23	3.0
General				
Fatigue†	56	12	58	6
Pyrexia	20	0.2	15	0
Metabolism and Nutrition				
Decreased appetite	28	1.5	30	0.5
Skin and Subcutaneous Tissue				
Rash‡	25	2.0	17	2.5
Respiratory, Thoracic and Mediastinal				
Cough	21	0	28	0
Dyspnea	21	3.7	26	5

* Graded per NCI CTCAE v4.03

† Includes asthenia and fatigue

‡ Includes genital rash, rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 13: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-189

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy		Placebo Pemetrexed Platinum Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Anemia	85	17	81	18
Lymphopenia	65	22	64	25
Neutropenia	50	21	41	19
Thrombocytopenia	30	12	29	8
Chemistry				
Hyperglycemia	63	9	60	7
Increased ALT	47	3.8	42	2.6
Increased AST	47	2.8	40	1.0
Hypoalbuminemia	39	2.8	39	1.1
Increased creatinine	37	4.2	25	1.0
Hyponatremia	32	7	23	6
Hypophosphatemia	30	10	28	14
Increased alkaline phosphatase	26	1.8	29	2.1
Hypocalcemia	24	2.8	17	0.5
Hyperkalemia	24	2.8	19	3.1
Hypokalemia	21	5	20	5

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab /pemetrexed/platinum chemotherapy (range: 381 to 401 patients) and placebo/pemetrexed/platinum chemotherapy (range: 184 to 197 patients).

† Graded per NCI CTCAE v4.03

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy

The safety of intravenous pembrolizumab in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in 558 patients with previously untreated, metastatic squamous NSCLC *[see Clinical Studies (14.4)]*. Safety data are available for the first 203 patients who received intravenous pembrolizumab and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to intravenous pembrolizumab was 7 months (range: 1 day to 12 months). Sixty-one percent of patients in the intravenous pembrolizumab arm were exposed to intravenous pembrolizumab for ≥6 months. A total of 139 of 203 patients (68%) received paclitaxel and 64 patients (32%) received paclitaxel protein-bound in combination with carboplatin.

The study population characteristics were: median age of 65 years (range: 40 to 83), 52% age 65 or older; 78% male; 83% White; and 9% with history of brain metastases.

Intravenous pembrolizumab was discontinued for adverse reactions in 15% of patients, with no single type of adverse reaction accounting for the majority. Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 43% of patients; the most common (≥2%) were thrombocytopenia (20%), neutropenia (11%), anemia (6%), asthenia (2%), and diarrhea (2%). The most frequent (≥2%) serious adverse reactions were febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

The adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs. 36%) and peripheral neuropathy (31% vs. 25%) were observed in the intravenous pembrolizumab and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

Previously Untreated NSCLC

The safety of intravenous pembrolizumab was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated Stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC *[see Clinical Studies (14.4)].* Patients received intravenous pembrolizumab 200 mg every 3 weeks (n=636) or investigator's choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to intravenous pembrolizumab was 5.6 months (range: 1 day to 27.3 months). Forty-eight percent of patients in the intravenous pembrolizumab arm were exposed to intravenous pembrolizumab 200 mg for ≥6 months.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Eighty-seven percent had metastatic disease (Stage IV), 13% had Stage III disease (2% Stage IIIA and 11% Stage IIIB), and 5% had treated brain metastases at baseline.

Intravenous pembrolizumab was discontinued for adverse reactions in 19% of patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were pneumonitis (3.0%), death due to unknown cause (1.6%), and pneumonia (1.4%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 33% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were pneumonitis (3.1%), pneumonia (3.0%), hypothyroidism (2.2%), and increased ALT (2.0%). The most frequent (≥2%) serious adverse reactions were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%).

Tables 14 and 15 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with intravenous pembrolizumab in KEYNOTE-042.

Table 14: Adverse Reactions Occurring in ≥10% of Patients in KEYNOTE-042

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks n=636		Chemotherapy n=615	
	All Grades* (%)	Grades 3-5 (%)	All Grades (%)	Grades 3-5 (%)
General				
Fatigue†	25	3.1	33	3.9
Pyrexia	10	0.3	8	0
Metabolism and Nutrition				
Decreased appetite	17	1.7	21	1.5
Respiratory, Thoracic and Mediastinal				
Dyspnea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Skin and Subcutaneous Tissue				
Rash‡	15	1.3	8	0.2
Gastrointestinal				
Constipation	12	0	21	0.2
Diarrhea	12	0.8	12	0.5
Nausea	12	0.5	32	1.1
Endocrine				
Hypothyroidism	12	0.2	1.5	0
Infections				
Pneumonia	12	7	9	6
Investigations				
Weight loss	10	0.9	7	0.2

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 15: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-042

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	4.7	51	5
Increased ALT	33	4.8	34	2.9
Hypoalbuminemia	33	2.2	29	1.0
Increased AST	31	3.6	32	1.7
Hyponatremia	31	9	32	8
Increased alkaline phosphatase	29	2.3	29	0.3
Hypocalcemia	25	2.5	19	0.7
Hyperkalemia	23	3.0	20	2.2
Increased prothrombin INR	21	2.0	15	2.9
Hypophosphatemia	20	4.7	17	4.3
Hematology				
Anemia	43	4.4	79	19
Lymphopenia	30	7	42	13

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 598 to 610 patients) and chemotherapy (range: 585 to 598 patients); increased prothrombin INR: intravenous pembrolizumab n=203 and chemotherapy n=173.
† Graded per NCI CTCAE v4.03

Previously Treated NSCLC

The safety of intravenous pembrolizumab was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations *[see Clinical Studies (14.4)]*. A total of

991 patients received intravenous pembrolizumab 2 mg/kg (n=339) or 10 mg/kg (n=343) every 3 weeks or docetaxel (n=309) at 75 mg/m^2 every 3 weeks. Patients with autoimmune disease, medical conditions that required systemic corticosteroids or other immunosuppressive medication, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to intravenous pembrolizumab 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to intravenous pembrolizumab 10 mg/kg every 3 weeks was 3.5 months (range: 1 day to 20.8 months). The data described below reflect exposure to intravenous pembrolizumab 2 mg/kg in 31% of patients exposed to intravenous pembrolizumab for ≥6 months. In the intravenous pembrolizumab 10 mg/kg arm, 34% of patients were exposed to intravenous pembrolizumab for ≥6 months.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; and 8% with advanced localized disease, 91% with metastatic disease, and 15% with history of brain metastases. Twenty-nine percent received two or more prior systemic treatments for advanced or metastatic disease.

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for adverse reactions in 8% of patients receiving intravenous pembrolizumab. The most common adverse events resulting in permanent discontinuation of intravenous pembrolizumab was pneumonitis (1.8%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-010.

Table 16: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-010

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

* Adverse reactions occurring at same or higher incidence than in docetaxel arm

† Graded per NCI CTCAE v4.0

‡ Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving intravenous pembrolizumab were fatigue (25%), diarrhea (14%), asthenia (11%) and pyrexia (11%).

Table 17: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving Intravenous Pembrolizumab in KEYNOTE-010

Laboratory Test†	Intravenous Pembrolizumab 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hyponatremia	32	8	27	2.9
Increased alkaline phosphatase	28	3.0	16	0.7
Increased AST	26	1.6	12	0.7
Increased ALT	22	2.7	9	0.4
Hypocalcemia	20	0.9	20	1.8

* 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: intravenous pembrolizumab (range: 631 to 638 patients) and docetaxel (range: 271 to 277 patients).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving intravenous pembrolizumab were hyperglycemia (44% all Grades; 4.1% Grades 3-4), anemia (37% all Grades; 3.8% Grades 3-4), hypertriglyceridemia (36% all Grades; 1.8% Grades 3-4), lymphopenia (32% all Grades; 9% Grades 3-4), hypoalbuminemia (34% all Grades; 1.6% Grades 3-4), and hypercholesterolemia (20% all Grades; 0.7% Grades 3-4).

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

The safety of intravenous pembrolizumab in combination with neoadjuvant platinum-containing chemotherapy followed by surgery and continued adjuvant treatment with intravenous pembrolizumab as a single agent after surgery was investigated in KEYNOTE-671, a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition *[see Clinical Studies (14.4)].* Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

The median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 10.9 months (range: 1 day to 18.6 months). The study population characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older, 7% age 75 or older; 71% male; 61% White, 31% Asian, 2% Black, 4% race not reported; 9% Hispanic or Latino.

Adverse reactions occurring in patients with resectable NSCLC receiving intravenous pembrolizumab in combination with platinum containing chemotherapy, given as neoadjuvant treatment and continued as single agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving intravenous pembrolizumab in combination with chemotherapy.

Neoadjuvant Phase of KEYNOTE-671

A total of 396 patients received at least 1 dose of intravenous pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment and 399 patients received at least 1 dose of placebo in combination with platinum-containing chemotherapy as neoadjuvant treatment.

Serious adverse reactions occurred in 34% of patients who received intravenous pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%).

Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received intravenous pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reactions that led to permanent discontinuation

of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the 396 intravenous pembrolizumab-treated patients and 399 placebo-treated patients who received neoadjuvant treatment, 6% (n=25) and 4.3% (n=17), respectively, did not receive surgery due to adverse reactions. The most frequent (≥1%) adverse reactions that led to cancellation of surgery in the intravenous pembrolizumab arm was interstitial lung disease (1%).

Of the 325 intravenous pembrolizumab-treated patients who received surgery, 3.1% (n=10) experienced delay of surgery (surgery more than 8 weeks from last neoadjuvant treatment if patient received less than 4 cycles of neoadjuvant therapy or more than 20 weeks after first dose of neoadjuvant treatment if patient received 4 cycles of neoadjuvant therapy) due to adverse reactions. Of the 317 placebo-treated patients who received surgery, 2.5% (n=8) experienced delay of surgery due to adverse reactions.

Of the 325 intravenous pembrolizumab-treated patients who received surgery, 7% (n=22) did not receive adjuvant treatment due to adverse reactions. Of the 317 placebo-treated patients who received surgery, 3.2% (n=10) did not receive adjuvant treatment due to adverse reactions.

Adjuvant Phase of KEYNOTE-671

A total of 290 patients in the intravenous pembrolizumab arm and 267 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent intravenous pembrolizumab as adjuvant treatment, 14% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of adjuvant intravenous pembrolizumab due to an adverse reaction occurred in 12% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant intravenous pembrolizumab were diarrhea (1.7%), interstitial lung disease (1.4%), AST increased (1%), and musculoskeletal pain (1%).

Adjuvant Treatment of Resected NSCLC

The safety of intravenous pembrolizumab as a single agent was investigated in KEYNOTE-091, a multicenter, randomized (1:1), triple-blind, placebo-controlled trial in patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC; adjuvant chemotherapy up to 4 cycles was optional *[see Clinical Studies (14.4)]*. A total of 1161 patients received intravenous pembrolizumab 200 mg (n=580) or placebo (n=581) every 3 weeks. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis.

The median duration of exposure to intravenous pembrolizumab was 11.7 months (range: 1 day to 18.9 months). Sixty-eight percent of patients in the intravenous pembrolizumab arm were exposed to intravenous pembrolizumab for ≥6 months.

The adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving intravenous pembrolizumab as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

Malignant Pleural Mesothelioma (MPM)

First-line treatment of unresectable advanced or metastatic MPM with pemetrexed and platinum chemotherapy

The safety of intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy (either carboplatin or cisplatin) was investigated in KEYNOTE-483, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with previously untreated, unresectable advanced or metastatic MPM *[see Clinical Studies (14.5)]*. A total of 473 patients received intravenous pembrolizumab 200 mg, pemetrexed, and platinum every 3 weeks for up to 6 cycles followed by intravenous pembrolizumab (n=241), or pemetrexed and platinum chemotherapy every 3 weeks for up to 6 cycles (n=232). Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible.

The median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 6.9 months (range: 1 day to 25.2 months). Sixty-one percent of patients in the intravenous pembrolizumab arm were exposed to intravenous pembrolizumab for ≥6 months.

Adverse reactions occurring in patients with MPM were generally similar to those in other patients receiving intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy.

HNSCC

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC

The safety of intravenous pembrolizumab as neoadjuvant and adjuvant treatment added to standard of care (SOC) therapy was evaluated in KEYNOTE-689, a multicenter, randomized (1:1), open-label, active-controlled trial in patients with resectable locally advanced (Stage III-IVA by AJCC 8th edition) head and neck squamous cell carcinoma (HNSCC) *[see Clinical Studies (14.6)].* Intravenous pembrolizumab was administered as single-agent neoadjuvant therapy before definitive surgery, during adjuvant radiotherapy (RT) with or without concurrent cisplatin, and then as single agent adjuvant therapy. Concurrent cisplatin was added to intravenous pembrolizumab and adjuvant RT for high-risk disease pathology. A total of 361 patients received treatment on the intravenous pembrolizumab arm and 315 patients received treatment on the SOC therapy arm.

The median duration of exposure to intravenous pembrolizumab in the neoadjuvant phase was 3.1 weeks (range: 1 day to 4.9 weeks). The median duration of exposure to intravenous pembrolizumab in the adjuvant phase was 42 weeks (range: 1 day to 82 weeks).

The median age of patients who received intravenous pembrolizumab was 60 years (range: 29 to 82), 32% age 65 or older, 6% age 75 or older; 79% male; 78% White, 14% Asian, 2.2% Black or African American, 2% Other races, 2.7% unknown race; and 15% Hispanic or Latino.

The most common adverse reactions (≥ 20%) on the intravenous pembrolizumab arm were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), dry mouth (22%), diarrhea (22%), and musculoskeletal pain (22%).

Table 18 and Table 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-689.

Table 18: Adverse Reactions in ≥20% of Patients with HNSCC Who Received Intravenous Pembrolizumab in KEYNOTE-689

Adverse Reaction	Intravenous Pembrolizumab Neoadjuvant then adjuvant beginning with RT with or without cisplatin n=361		Standard of Care Adjuvant RT with or without cisplatin n=315	
	All Grades* (%)	Grade 3 or 4 (%)	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal				
Stomatitis†	48	14	60	13
Dysphagia	29	12	32	11
Constipation	27	0.3	22	0.3
Nausea	24	1.9	28	2.9
Dry mouth	22	1.4	26	1.6
Diarrhea‡	22	4.2	11	0.6
Injury, poisoning and procedural complications				
Radiation skin injury	40	4.2	48	5.7
Investigations				
Weight loss	36	14	27	10
Endocrine disorders				
Hypothyroidism§	26	0	6	0
General				

Fatigue[¶]	33	2.2	27	1.6
Skin and subcutaneous tissue disorders				
Rash[#]	22	1.9	10	1.9
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[Þ]	22	1.9	16	0.6

* Graded per NCI CTCAE v4.03
† Includes pharyngeal inflammation, cheilitis, oral mucosal erythema, mucosal inflammation, glossitis, mouth ulceration, tongue ulceration
‡ Includes colitis, enteritis, hemorrhagic diarrhea
§ Includes blood thyroid stimulating hormone increased
¶ Includes asthenia
# Includes dermatitis, skin exfoliation, dermatitis acneiform, eczema, rash macular, rash maculo-papular, erythema multiforme, dermatitis exfoliative, urticarial dermatitis, eczema asteatotic, exfoliative rash, rash pruritic, rash pustular
Þ Includes neck pain, arthralgia, pain in extremity, back pain, myalgia, bone pain, arthritis, non-cardiac chest pain, musculoskeletal chest pain, musculoskeletal stiffness, spinal pain

Table 19: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with HNSCC Who Received Intravenous Pembrolizumab in KEYNOTE-689

Laboratory Test*	Intravenous Pembrolizumab Neoadjuvant then adjuvant beginning with radiation with or without cisplatin		Radiation with or without cisplatin	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	76	50	86	55
Anemia	75	12	74	12
Neutropenia	32	13	35	19
Thrombocytopenia	22	1.7	29	1.9
Chemistry				
Hyperglycemia	57	5.7	47	2.7
Hyponatremia	47	16	36	11
Increased ALT	42	6.2	37	2.0
Hypoalbuminemia	40	1.4	38	1.0
Increased AST	38	4.8	23	2.0
Hypomagnesemia	34	1.2	22	1.3
Hypokalemia	29	6.8	20	7.4
Hyperkalemia	29	3.4	24	2.3
Increased alkaline phosphatase	27	2.5	19	0.0
Hypocalcemia	27	2.6	26	3.3
Hypophosphatemia	23	6.1	15	7.0
Increased creatinine	22	2.0	27	2.9
Hypercalcemia	21	2.0	14	1.3

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Intravenous Pembrolizumab + CRT/RT (range: 342 to 357 patients) and CRT/RT (range: 300 to 309 patients)
† Graded per NCI CTCAE v4.03

Neoadjuvant Phase of KEYNOTE-689

Of the 361 patients who received at least one dose of single agent intravenous pembrolizumab as neoadjuvant treatment, 11% of patients experienced serious adverse reactions. Serious adverse reactions that occurred in more than one patient were pneumonia (1.4%), tumor hemorrhage (0.8%), dysphagia (0.6%), immune mediated hepatitis (0.6%), cellulitis (0.6%), and dyspnea (0.6%). Fatal adverse reactions occurred in 1.1% of patients who received neoadjuvant intravenous pembrolizumab including respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each).

Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 2.8% of patients who received intravenous pembrolizumab as neoadjuvant treatment. The most frequent adverse reaction which resulted in permanent discontinuation of neoadjuvant intravenous pembrolizumab in more than one patient was arthralgia (0.6%).

Of the 361 patients who received intravenous pembrolizumab as neoadjuvant treatment, 11% (n=38) did not receive surgery. Surgical cancellation on the intravenous pembrolizumab arm was due to disease progression in 4% (n=15), patient decision in 3% (n=10), adverse reactions in 1.4% (n=5), physician's decision in 1.1% (n=4), unresectable tumor in 0.6% (n=2), loss of follow-up in 0.3% (n=1), and use of non-study anti-cancer therapy in 0.3% (n=1).

Of the 351 patients randomized to SOC, 12% (n=43) did not receive surgery. Surgical cancellation on the SOC arm was due to patient decision in 7% (n=24), physician's decision in 2.3% (n=8), disease progression in 1.7% (n=6), and adverse reactions in 1.4% (n=5).

Of the 323 intravenous pembrolizumab-treated patients who received surgery, 1.2% (n=4) experienced delay of surgery (defined as on-study surgery occurring ≥ 9 weeks after initiation of neoadjuvant intravenous pembrolizumab) due to adverse reactions. Of the 307 patients randomized to SOC who received surgery on study, 0.3% (n=1) experienced delay of surgery (defined as surgery occurring ≥ 6 weeks after randomization) due to adverse reactions.

Among the intravenous pembrolizumab-treated patients who received surgery, 2.8% (n=9) did not receive adjuvant treatment due to adverse reactions. Among the SOC-treated patients who received surgery, 3.6% (n=11) did not receive adjuvant RT or chemoradiation due to adverse reactions.

Adjuvant Phase of KEYNOTE-689

A total of 275 patients in the intravenous pembrolizumab arm and 275 patients in the SOC arm started the adjuvant phase of treatment. On the intravenous pembrolizumab arm, 100 patients received intravenous pembrolizumab and cisplatin with concurrent RT, 154 patients received intravenous pembrolizumab alone with concurrent RT, 7 patients received cisplatin alone with concurrent RT, and 13 patients received RT alone. One patient received intravenous pembrolizumab alone. On the SOC arm, 139 patients received cisplatin with concurrent RT while 136 patients received RT alone. For the intravenous pembrolizumab arm, a total of 222 patients received single-agent intravenous pembrolizumab following RT.

Of the 255 patients who received at least one dose of intravenous pembrolizumab in the adjuvant phase, 38% experienced serious adverse reactions. The most frequent serious adverse reactions reported in ≥1% of intravenous pembrolizumab-treated patients were pneumonia (2.7%), pyrexia (2.4%), stomatitis (2.4%), acute kidney injury (2.0%), pneumonitis (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhea (1.2%), dysphagia (1.2%), gastrostomy tube site complication (1.2%), and immune-mediated hepatitis (1.2%).

Fatal adverse reactions occurred in 5% including death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%) and gastrointestinal hemorrhage (0.4%).

Permanent discontinuation of adjuvant intravenous pembrolizumab due to an adverse reaction occurred in 17% of patients. The most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant intravenous pembrolizumab were pneumonitis, colitis, immune-mediated hepatitis and death not otherwise specified.

Of the 275 patients who received SOC in the adjuvant phase, 23% experienced serious adverse reactions.

The most frequent serious adverse reactions reported in >1% of SOC-treated patients were pneumonia (3.6%) and acute kidney injury (3.3%). Fatal adverse reactions occurred in 4.7% including pneumonia (0.7%), septic shock (0.4%), death not otherwise specified (0.4%), sudden death (0.4%), myocardial infarction (0.4%), pancreatic neoplasm (0.4%) and other infections (2.9%).

First-line treatment of metastatic or unresectable, recurrent HNSCC

The safety of intravenous pembrolizumab, as a single agent and in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, was investigated in KEYNOTE-048, a multicenter, open-label, randomized (1:1:1), active-controlled trial in patients with previously untreated, recurrent or metastatic HNSCC *[see Clinical Studies (14.6)]*. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. A total of 576 patients received intravenous pembrolizumab 200 mg every 3 weeks either as a single agent (n=300) or in combination with platinum and FU (n=276) every 3 weeks for 6 cycles followed by intravenous pembrolizumab, compared to 287 patients who received cetuximab weekly in combination with platinum and FU every 3 weeks for 6 cycles followed by cetuximab.

The median duration of exposure to intravenous pembrolizumab was 3.5 months (range: 1 day to 24.2 months) in the intravenous pembrolizumab single agent arm and was 5.8 months (range: 3 days to 24.2 months) in the combination arm. Seventeen percent of patients in the intravenous pembrolizumab single agent arm and 18% of patients in the combination arm were exposed to intravenous pembrolizumab for ≥12 months. Fifty-seven percent of patients receiving intravenous pembrolizumab in combination with chemotherapy started treatment with carboplatin.

Intravenous pembrolizumab was discontinued for adverse reactions in 12% of patients in the intravenous pembrolizumab single agent arm. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were sepsis (1.7%) and pneumonia (1.3%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 31% of patients; the most common adverse reactions leading to interruption of intravenous pembrolizumab (≥2%) were pneumonia (2.3%), pneumonitis (2.3%), and hyponatremia (2%).

Intravenous pembrolizumab was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 45% of patients; the most common adverse reactions leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 20 and 21 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-048.

Table 20: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-048

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks n=300		Intravenous Pembrolizumab 200 mg every 3 weeks Platinum FU n=276		Cetuximab Platinum FU n=287	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General						
Fatigue[†]	33	4	49	11	48	8
Pyrexia	13	0.7	16	0.7	12	0
Mucosal inflammation	4.3	1.3	31	10	28	5
Gastrointestinal						
Constipation	20	0.3	37	0	33	1.4
Nausea	17	0	51	6	51	6
Diarrhea[‡]	16	0.7	29	3.3	35	3.1
Vomiting	11	0.3	32	3.6	28	2.8
Dysphagia	8	2.3	12	2.9	10	2.1
Stomatitis	3	0	26	8	28	3.5
Skin						
Rash[§]	20	2.3	17	0.7	70	8
Pruritus	11	0	8	0	10	0.3
Respiratory, Thoracic and Mediastinal						
Cough[¶]	18	0.3	22	0	15	0
Dyspnea[#]	14	2.0	10	1.8	8	1.0
Endocrine						
Hypothyroidism	18	0	15	0	6	0
Metabolism and Nutrition						
Decreased appetite	15	1.0	29	4.7	30	3.5
Weight loss	15	2	16	2.9	21	1.4
Infections						
Pneumonia[Þ]	12	7	19	11	13	6
Nervous System						
Headache	12	0.3	11	0.7	8	0.3
Dizziness	5	0.3	10	0.4	13	0.3
Peripheral sensory neuropathy[ß]	1	0	14	1.1	7	1
Musculoskeletal						
Myalgia[à]	12	1.0	13	0.4	11	0.3
Neck pain	6	0.7	10	1.1	7	0.7
Psychiatric						
Insomnia	7	0.7	10	0	8	0

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

§ Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, seborrheic dermatitis

¶ Includes cough, productive cough

Includes dyspnea, exertional dyspnea

Þ Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal

ß Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia

à Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

Table 21: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-048

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks		Intravenous Pembrolizumab 200 mg every 3 weeks Platinum FU		Cetuximab Platinum FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology						
Lymphopenia	54	25	70	35	75	46
Anemia	52	7	89	29	79	20
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	8	1.4	68	37	73	43
Chemistry						
Hyperglycemia	47	3.8	54	6	65	4.7
Hyponatremia	46	18	55	20	59	20
Hypoalbuminemia	44	3.5	46	3.9	49	1.1
Increased AST	28	3.1	25	1.9	37	3.6
Increased ALT	25	2.1	22	1.5	38	1.8
Increased alkaline phosphatase	25	2.1	26	1.1	33	1.1
Hypercalcemia	22	4.5	16	4.2	13	2.5
Hypocalcemia	22	1.0	32	3.8	58	6
Hyperkalemia	21	2.8	28	4.2	29	4.6
Hypophosphatemia	20	5	34	12	49	20
Hypokalemia	19	5	33	12	47	15
Increased creatinine	17	1.0	36	2.3	27	2.1
Hypomagnesemia	15	0.4	40	1.7	76	9

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab/chemotherapy (range: 240 to 267 patients), intravenous pembrolizumab (range: 245 to 292 patients), cetuximab/chemotherapy (range: 249 to 282 patients).

† Graded per NCI CTCAE v4.0

Previously treated recurrent or metastatic HNSCC

Among the 192 patients with HNSCC enrolled in KEYNOTE-012 *[see Clinical Studies (14.6)]*, the median duration of exposure to intravenous pembrolizumab was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for KEYNOTE-012.

The study population characteristics were: median age of 60 years (range: 20 to 84), 35% age 65 or older; 83% male; and 77% White, 15% Asian, and 5% Black. Sixty-one percent of patients had two or more lines of therapy in the recurrent or metastatic setting, and 95% had prior radiation therapy. Baseline ECOG PS was 0 (30%) or 1 (70%) and 86% had M1 disease.

Intravenous pembrolizumab was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving intravenous pembrolizumab. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); therefore, summary safety results are provided in a pooled analysis. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.1)]*.

Urothelial Cancer

Patients with urothelial cancer in combination with enfortumab vedotin-ejfv

The safety of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv was investigated in KEYNOTE-A39 in patients with locally advanced or metastatic urothelial cancer *[see Clinical Studies (14.7)].* A total of 440 patients received intravenous pembrolizumab 200 mg on Day 1 and enfortumab vedotin-ejfv 1.25 mg/kg on Days 1 and 8 of each 21-day cycle compared to 433 patients who received gemcitabine on Days 1 and 8 and investigator's choice of cisplatin or carboplatin on Day 1 of each 21-day cycle. Among patients who received intravenous pembrolizumab and enfortumab vedotin-ejfv, the median duration of exposure to intravenous pembrolizumab was 8.5 months (range: 9 days to 28.5 months).

Fatal adverse reactions occurred in 3.9% of patients treated with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Serious adverse reactions occurred in 50% of patients receiving intravenous pembrolizumab in combination with enfortumab vedotin-ejfv. Serious adverse reactions in ≥2% of patients receiving intravenous pembrolizumab in combination with enfortumab vedotin-ejfv were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Permanent discontinuation of intravenous pembrolizumab occurred in 27% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of intravenous pembrolizumab were pneumonitis/ILD (4.8%) and rash (3.4%).

Dose interruptions of intravenous pembrolizumab occurred in 61% of patients. The most common adverse reactions (≥2%) resulting in interruption of intravenous pembrolizumab were rash (17%), peripheral neuropathy (7%), COVID-19 (5%), diarrhea (4.3%), pneumonitis/ILD (3.6%), neutropenia (3.4%), fatigue (3%), alanine aminotransferase increased (2.7%), hyperglycemia (2.5%), pneumonia (2%), and pruritus (2%).

Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in combination with enfortumab vedotin-ejfv in KEYNOTE-A39.

Table 22: Adverse Reactions ≥20% (All Grades) in Patients Treated with Intravenous Pembrolizumab in Combination with Enfortumab Vedotin-ejfv in KEYNOTE-A39

Adverse Reaction	Intravenous Pembrolizumab in combination with Enfortumab Vedotin-ejfv n=440		Chemotherapy n=433	
	All Grades* %	Grades 3-4 %	All Grades* %	Grades 3-4 %
Skin and subcutaneous tissue disorders				
Rash†	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
General disorders and administration site conditions				
Fatigue†	51	6	57	7
Nervous system disorders				
Peripheral neuropathy†	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Weight loss	33	3.6	9	0.2
Eye disorders				
Dry eye†	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

* Graded per NCI CTCAE v4.03
† Includes multiple terms

Clinically relevant adverse reactions (<20%) include pyrexia (18%), dry skin (17%), vomiting (12%), pneumonitis/ILD (10%), hypothyroidism (10%), blurred vision (6%), infusion site extravasation (2%), and myositis (0.5%).

Table 23: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-A39

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks and Enfortumab Vedotin-ejfv		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased aspartate aminotransferase	75	4.6	39	3.3
Increased creatinine	71	3.2	68	2.6
Hyperglycemia	66	14	54	4.7
Increased alanine aminotransferase	59	5	49	3.3
Hyponatremia	46	13	47	13
Hypophosphatemia	44	9	36	9
Hypoalbuminemia	39	1.8	35	0.5
Hypokalemia	26	5	16	3.1
Hyperkalemia	24	1.4	36	4.0
Hypercalcemia	21	1.2	14	0.2
Hematology				
Lymphopenia	58	15	59	17
Anemia	53	7	89	33
Neutropenia	30	9	80	50

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 407 to 439 patients)

† Graded per NCI CTCAE v4.03

Cisplatin-ineligible patients with urothelial cancer in combination with enfortumab vedotin-ejfv

The safety of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv was investigated in KEYNOTE-869 in patients with locally advanced or metastatic urothelial cancer and who are not eligible for cisplatin-based chemotherapy *[see Clinical Studies (14.7)]*. A total of 121 patients received intravenous pembrolizumab 200 mg on Day 1, and enfortumab vedotin-ejfv 1.25 mg/kg on days 1 and 8 of each 21-day cycle. The median duration of exposure to intravenous pembrolizumab was 6.9 months (range: 1 day to 29.6 months).

Fatal adverse reactions occurred in 5% of patients treated with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis (0.8%).

Serious adverse reactions occurred in 50% of patients receiving intravenous pembrolizumab and enfortumab vedotin-ejfv. Serious adverse reactions in ≥2% of patients receiving intravenous pembrolizumab in combination with enfortumab vedotin-ejfv were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), hematuria (3.3%), pneumonia (3.3%), pneumonitis (3.3%), sepsis (3.3%), anemia (2.5%), diarrhea (2.5%), hypotension (2.5%), myasthenia gravis (2.5%), myositis (2.5%), and urinary retention (2.5%).

Permanent discontinuation of intravenous pembrolizumab occurred in 32% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of intravenous pembrolizumab were pneumonitis (5%), peripheral neuropathy (5%), rash (3.3%), and myasthenia gravis (2.5%).

Dose interruptions of intravenous pembrolizumab occurred in 69% of patients. The most common adverse reactions (≥2%) resulting in interruption of intravenous pembrolizumab were peripheral neuropathy (22%), rash (17%), neutropenia (7%), fatigue (6%), diarrhea (5%), lipase increased (5%), acute kidney injury (3.3%), ALT increased (2.5%), and COVID-19 (2.5%).

Tables 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in combination with enfortumab vedotin-ejfv in KEYNOTE-869.

Table 24: Adverse Reactions Occurring in ≥20% of Patients Treated with Intravenous Pembrolizumab in Combination with Enfortumab Vedotin-ejfv in KEYNOTE-869

Adverse Reaction	Intravenous Pembrolizumab in combination with Enfortumab Vedotin-ejfv n=121	
	All Grades* %	Grade 3-4 %
Skin and subcutaneous tissue disorders		
Rash†	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy‡	65	3.3
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Weight loss	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

* Graded per NCI CTCAE v4.03

† Includes: blister, conjunctivitis, dermatitis, dermatitis bullous, dermatitis exfoliative generalized, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin exfoliation, and stomatitis

‡ Includes: dysesthesia, hypoesthesia, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and gait disturbance

Clinically relevant adverse reactions (<20%) include vomiting (19.8%), fever (18%), hypothyroidism (11%), pneumonitis/ILD (10%), myositis (3.3%), myasthenia gravis (2.5%), and infusion site extravasation (0.8%).

Table 25: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-869

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks and Enfortumab Vedotin-ejfv	
	All Grades† %	Grades 3-4 %
Chemistry		
Hyperglycemia	74	13
Increased aspartate aminotransferase	73	9
Increased creatinine	69	3.3
Hyponatremia	60	19
Increased alanine aminotransferase	60	7
Increased lipase	59	32
Hypoalbuminemia	59	4.2
Hypophosphatemia	51	15
Hypokalemia	35	8
Increased potassium	27	1.7
Increased calcium	27	4.2
Hematology		
Anemia	69	15
Lymphopenia	64	17
Neutropenia	32	12

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 114 to 121 patients)

† Graded per NCI CTCAE v4.03

Platinum-Ineligible Patients with Urothelial Carcinoma

The safety of intravenous pembrolizumab was investigated in KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who had one or more comorbidities. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible *[see Clinical Studies (14.7)]*. Patients received intravenous pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression.

The median duration of exposure to intravenous pembrolizumab was 2.8 months (range: 1 day to 15.8 months).

Intravenous pembrolizumab was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with intravenous pembrolizumab experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥40 mg oral prednisone equivalent.

Table 26 summarizes adverse reactions in patients on intravenous pembrolizumab in KEYNOTE-052.

Table 26: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-052

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks N=370	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	38	6
Pyrexia	11	0.5
Weight loss	10	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain‡	24	4.9
Arthralgia	10	1.1
Metabolism and Nutrition		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Gastrointestinal		
Constipation	21	1.1
Diarrhea§	20	2.4
Nausea	18	1.1
Abdominal pain¶	18	2.7
Elevated LFTs#	13	3.5
Vomiting	12	0
Skin and Subcutaneous Tissue		
Rashᵖ	21	0.5
Pruritus	19	0.3
Edema peripheralᵝ	14	1.1
Infections		
Urinary tract infection	19	9
Blood and Lymphatic System		
Anemia	17	7
Respiratory, Thoracic, and Mediastinal		
Cough	14	0
Dyspnea	11	0.5
Renal and Urinary		
Increased blood creatinine	11	1.1
Hematuria	13	3.0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
§ Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
¶ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
# Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests
ᵖ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized
ᵝ Includes edema peripheral, peripheral swelling

Previously Treated Urothelial Carcinoma

The safety of intravenous pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received intravenous pembrolizumab 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.7)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible.

The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received intravenous pembrolizumab and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

Intravenous pembrolizumab was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab was pneumonitis (1.9%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). Serious adverse reactions occurred in 39% of intravenous pembrolizumab-treated patients. The most frequent serious adverse reactions (≥2%) in intravenous pembrolizumab-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-045.

Table 27: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-045

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks n=266		Chemotherapy* n=255	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain§	32	3.0	27	2.0
Skin and Subcutaneous Tissue				
Pruritus	23	0	6	0.4
Rash¶	20	0.4	13	0.4
Gastrointestinal				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea#	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
Metabolism and Nutrition				
Decreased appetite	21	3.8	21	1.2
Infections				
Urinary tract infection	15	4.9	14	4.3
Respiratory, Thoracic and Mediastinal				
Cough Þ	15	0.4	9	0
Dyspnea ß	14	1.9	12	1.2
Renal and Urinary				
Hematuria à	12	2.3	8	1.6

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes asthenia, fatigue, malaise, lethargy
§ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
¶ Includes rash maculo-papular, rash, genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrheic keratosis, lichenoid keratosis
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes cough, productive cough
ß Includes dyspnea, dyspnea exertional, wheezing
à Includes blood urine present, hematuria, chromaturia

Table 28: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving Intravenous Pembrolizumab in KEYNOTE-045

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	8	60	7
Anemia	52	13	68	18
Lymphopenia	45	15	55	26
Hypoalbuminemia	43	1.7	50	3.8
Hyponatremia	37	9	47	13
Increased alkaline phosphatase	37	7	33	4.9
Increased creatinine	35	4.4	28	2.9
Hypophosphatemia	29	8	34	14
Increased AST	28	4.1	20	2.5
Hyperkalemia	28	0.8	27	6
Hypocalcemia	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: intravenous pembrolizumab n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0

Neoadjuvant and Adjuvant Treatment of Patients Who are Cisplatin-Eligible with MIBC in Combination with Enfortumab Vedotin-ejfv

The safety of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as neoadjuvant treatment and continued after radical cystectomy (RC) as adjuvant treatment was investigated in KEYNOTE-B15, an open-label, multicenter, randomized, active-controlled trial in patients with previously untreated MIBC who were eligible for cisplatin-based chemotherapy. Patients received intravenous pembrolizumab in combination with enfortumab vedotin-ejfv (n=403) before and after RC with pelvic lymph node dissection (PLND) or chemotherapy (gemcitabine with cisplatin) before RC with PLND followed by observation (n=396) *[see Clinical Studies (14.7)]*.

For the 403 patients who received intravenous pembrolizumab in the neoadjuvant phase, the median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 2.1 months (range: 1 day to 3.9 months) and the median number of cycles of intravenous pembrolizumab was 4 (range: 1 to 4) out of the planned 4 cycles in the neoadjuvant phase. For the 262 patients randomized to receive intravenous pembrolizumab in combination with enfortumab vedotin-ejfv and who received any adjuvant treatment, 249 patients received intravenous pembrolizumab in the adjuvant phase. The median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 8.3 months (range: 1 day to 18.9 months) and the median number of cycles of intravenous pembrolizumab was 13 (range: 1 to 13) out of the planned 13 cycles for patients who received intravenous pembrolizumab in the adjuvant phase. Across the combined neoadjuvant and adjuvant phases (n=403), the median number of cycles of intravenous pembrolizumab was 10 (range: 1 to 17) out of the planned 17 cycles. Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in combination with enfortumab vedotin-ejfv in KEYNOTE-B15.

Table 29: Adverse Reactions ≥20% (All Grades) in Patients Treated with Intravenous Pembrolizumab in Combination with Enfortumab Vedotin-ejfv in KEYNOTE-B15

Adverse Reaction	Perioperative Intravenous Pembrolizumab 200 mg every 3 weeks in combination with Enfortumab Vedotin-ejfv n=403		Neoadjuvant Gemcitabine with Cisplatin n=396	
	All Grades* %	Grade 3-4 %	All Grades* %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash†	63	12	9	0.3
Pruritus	46	3.2	4.5	0
Alopecia	32	0.5	11	0
General disorders and administration site conditions				

Adverse Reaction	Perioperative Intravenous Pembrolizumab 200 mg every 3 weeks in combination with Enfortumab Vedotin-ejfv n=403		Neoadjuvant Gemcitabine with Cisplatin n=396	
	All Grades* %	Grade 3-4 %	All Grades* %	Grade 3-4 %
Fatigue†	48	2.7	49	2.3
Nervous system disorders				
Peripheral neuropathy†	43	3	11	0.8
Dysgeusia†	28	0.2	10	0
Gastrointestinal disorders				
Diarrhea†	36	3.2	16	1.3
Nausea	28	1	47	0.5
Constipation	27	0.7	37	0.5
Metabolism and nutrition disorders				
Decreased appetite	29	1	18	0.5
Hyperglycemia†	20	7	7	0.8
Infections and infestations				
Urinary tract infection	25	10	21	10
Eye Disorders				
Dry eye†	25	0	1.3	0
Investigations				
Weight loss	22	2.5	6	0.3

*Graded per NCI CTCAE v5.0
† Includes multiple terms.

Clinically relevant adverse reactions (<20%) include dry skin (16%), vomiting (13%), hypothyroidism (12%), pneumonitis/ILD (8%), skin hyperpigmentation (3.5%), myositis (0.7%), infusion site extravasation (0.5%), and myasthenia gravis (0.2%).

Table 30: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Treated with Intravenous Pembrolizumab in Combination with Enfortumab Vedotin-ejfv in KEYNOTE-B15

Laboratory Test*	Perioperative Intravenous Pembrolizumab 200 mg every 3 weeks in combination with Enfortumab Vedotin-ejfv n=403		Neoadjuvant Gemcitabine with Cisplatin n=396	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Decreased hemoglobin	70	8	92	20
Decreased lymphocytes	52	17	46	11
Decreased neutrophils	32	13	75	40
Chemistry				
Increased AST	69	7	23	0.5
Increased ALT	67	8	30	0
Increased creatinine	49	8	53	6
Decreased sodium	43	4.2	39	1.3
Decreased albumin	42	3.3	36	1.8
Increased potassium	35	4.7	31	5
Decreased potassium	22	3	20	2.8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab in combination with enfortumab vedotin-ejfv (range: 399 to 403 patients), and chemotherapy alone (range: 388 to 393 patients).

† Graded per NCI CTCAE v5.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Neoadjuvant Phase of KEYNOTE-B15

A total of 403 patients received at least 1 dose of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as neoadjuvant treatment before receiving RC.

In the neoadjuvant phase, serious adverse reactions occurred in 27% of patients who received intravenous pembrolizumab in combination with enfortumab vedotin-ejfv. The most frequent (≥ 1.5%) serious adverse reactions were rash (3.2%), pneumonitis/ILD (2.2%), and diarrhea (1.7%). Fatal adverse reactions occurred in 1.7% of patients, including multiple organ dysfunction syndrome (0.5%), and COVID-19 pneumonia, cardiac arrest, pneumonia, septic shock, and urosepsis (0.2% each). Additional fatal adverse reactions were reported in 2 patients in the post-surgery phase before adjuvant treatment started, including pneumonia and sepsis (1 patient each).

Permanent discontinuation of intravenous pembrolizumab in the neoadjuvant phase due to an adverse reaction occurred in 17% of patients. The most frequent (>1%) adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were rash (2.2%), increased ALT and pneumonitis/ILD (1.7% each), and hepatitis (1.2%).

Adverse reactions leading to dose interruption of intravenous pembrolizumab in the neoadjuvant phase occurred in 29% of patients. The most common adverse reactions (≥2%) leading to dose interruption of intravenous pembrolizumab were rash (8%), increased ALT (3.7%), neutropenia (3.2%), and hyperglycemia (2.5%). Of the 403 patients in the intravenous pembrolizumab in combination with enfortumab vedotin-ejfv arm who received neoadjuvant treatment, 13 patients (3.2%) did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery were multiple organ dysfunction syndrome (0.5%) and adenocarcinoma of colon, COVID-19 pneumonia, cardiac arrest,

chronic obstructive pulmonary disease, coronary artery disease, glomerulonephritis, immune-mediated lung disease, myocarditis, pneumonia, pneumonitis and urosepsis (0.2% each).

Of the 351 patients who received neoadjuvant treatment with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv and underwent radical cystectomy, 26 (7%) patients experienced delay of surgery (defined as time from last neoadjuvant treatment to surgery exceeding 8 weeks) due to adverse reactions.

Adjuvant Phase of KEYNOTE-B15

Patients who did not proceed to surgery were ineligible for adjuvant therapy. Of the 351 patients who received neoadjuvant treatment and underwent surgery, 249 patients received adjuvant treatment with intravenous pembrolizumab with or without enfortumab vedotin-ejfv. Of the 102 patients who did not receive adjuvant intravenous pembrolizumab, discontinuation of intravenous pembrolizumab prior to the adjuvant phase was due to an adverse event in 57 patients.

In the adjuvant phase, serious adverse reactions occurred in 35% of patients who received intravenous pembrolizumab in the adjuvant phase; the most frequent (≥1.5%) serious adverse reactions were urinary tract infection (8%), sepsis (2.8%), diarrhea, hyperglycemia, and pneumonitis/ILD (1.6% each). Fatal adverse reactions occurred in 3.2% of patients who received intravenous pembrolizumab in the adjuvant phase, including death (0.8%) and cardiac arrest, duodenal ulcer perforation, acute pancreatitis, renal failure, small cell lung cancer and toxic shock syndrome (0.4% each).

Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 23% of patients who received intravenous pembrolizumab in the adjuvant phase. The most frequent (>1%) adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were diarrhea and pneumonitis/ILD (2.4% each), rash (2%), and hyperglycemia and sepsis (1.2% each).

Adverse reactions leading to dose interruption of intravenous pembrolizumab in the adjuvant phase occurred in 39% of patients who received intravenous pembrolizumab in the adjuvant phase. The most common adverse reactions (≥2%) leading to dose interruption of intravenous pembrolizumab were diarrhea (6%), urinary tract infection (5%), COVID-19 (3.6%), rash (2.8%), and nausea (2%).

Neoadjuvant and Adjuvant Treatment of Patients Who are Cisplatin-Ineligible with MIBC in Combination with Enfortumab Vedotin-ejfv

The safety of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as neoadjuvant treatment and continued after radical cystectomy (RC) as adjuvant treatment was investigated in KEYNOTE-905, an open-label, multicenter, randomized, active-controlled trial in patients with previously untreated MIBC who were ineligible for or declined cisplatin-based chemotherapy. Patients received intravenous pembrolizumab in combination with enfortumab vedotin-ejfv (n=167) before and after RC with pelvic lymph node dissection (PLND) or RC with PLND alone (n=159) *[see Clinical Studies (14.7)]*.

For the 167 patients who received intravenous pembrolizumab in the neoadjuvant phase, the median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 1.4 months (range: 1 day to 2.7 months) and the median number of cycles of intravenous pembrolizumab was 3 (range: 1 to 3) out of the planned 3 cycles in the neoadjuvant phase. For the 100 patients randomized to receive intravenous pembrolizumab in combination with enfortumab vedotin-ejfv and who received any adjuvant treatment, 96 patients received intravenous pembrolizumab in the adjuvant phase. The median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 8.5 months (range: 1 day to 12.9 months) and the median number of cycles of intravenous pembrolizumab was 12 (range: 1 to 14) out of the planned 14 cycles for patients who received intravenous pembrolizumab in the adjuvant phase. Across the combined neoadjuvant and adjuvant phases (n=167), the median number of cycles of intravenous pembrolizumab was 5 (range: 1 to 17) out of the planned 17 cycles.

Tables 31 and 32 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in combination with enfortumab vedotin-ejfv in KEYNOTE-905.

Table 31: Adverse Reactions ≥20% (All Grades) in Patients Treated with Intravenous Pembrolizumab in Combination with Enfortumab Vedotin-ejfv in KEYNOTE-905

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks in combination with enfortumab vedotin-ejfv before and after RC with PLND n=167		RC with PLND alone n=159	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash*,†	54	7	1.3	0
Pruritus	47	3	0	0
Alopecia	35	0.6	0	0
General disorders and administration site conditions				
Fatigue*	47	4.2	6	0.6
Nervous system disorders				
Peripheral neuropathy*	39	3	1.9	0
Dysgeusia*	35	0	0	0
Gastrointestinal disorders				
Diarrhea*	34	5	3.1	1.3
Constipation	28	1.8	8	0
Nausea	26	1.2	8	0.6
Metabolism and nutrition disorders				
Decreased appetite	28	0.6	1.9	0
Infections and infestations				
Urinary tract infection	24	12	13	11
Eye disorders				
Dry eye*	21	0	0	0
Investigations				
Weight loss	20	0	3.1	0

*Includes multiple terms.

†Includes rash, rash maculo-papular, conjunctivitis, erythema, eczema, skin exfoliation, palmar-plantar erythrodysesthesia syndrome, blister, dermatitis, dermatitis exfoliative generalized, exfoliative rash, rash papular, rash pruritic, dermatitis bullous, drug eruption, pemphigoid, rash vesicular, and dermatitis contact.

Clinically relevant adverse reactions (<20%) include dry skin (15%), hypothyroidism (14%), vomiting (9%), pneumonitis/ILD (4.2%), skin hyperpigmentation (3.0%), infusion site extravasation (1.2%), and myasthenia gravis and myositis (0.6% each).

Table 32: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Treated with Intravenous Pembrolizumab in Combination with Enfortumab Vedotin-ejfv in KEYNOTE-905

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks in combination with enfortumab vedotin-ejfv before and after RC with PLND n=167		RC with PLND alone n=159	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased glucose	72	12	24	1.7
Increased AST	55	6	11	1.8
Increased ALT	53	4.8	13	0.9
Increased creatinine	47	8	31	2.5
Decreased sodium	44	13	18	7
Increased potassium	39	7	20	6
Decreased phosphate	26	6	1.8	0
Hematology				
Decreased hemoglobin	60	13	48	8
Decreased lymphocytes	40	8	17	1.7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Intravenous pembrolizumab in combination with enfortumab vedotin-ejfv (167 patients), and RC and PLND alone (range: 110 to 121 patients).

† Graded per NCI CTCAE v4.03

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Neoadjuvant Phase of KEYNOTE-905

A total of 167 patients received at least 1 dose of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as neoadjuvant treatment before receiving RC.

In the neoadjuvant phase, serious adverse reactions occurred in 27% of patients receiving intravenous pembrolizumab in combination with enfortumab vedotin-ejfv. The most frequent (≥2%) serious adverse reactions were urinary tract infection (3.6%) and hematuria (2.4%). Fatal adverse reactions occurred in 1.2% of patients, including myasthenia gravis and toxic epidermal necrolysis (0.6% each). Additional fatal adverse reactions were reported in 2.7% of patients in the post-surgery phase before adjuvant treatment started, including sepsis and intestinal obstruction (1.4% each).

Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 15% of patients. The most frequent (>1%) adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were rash (2.4%, including generalized exfoliative dermatitis), increased alanine aminotransferase, increased aspartate aminotransferase, diarrhea, dysgeusia, and toxic epidermal necrolysis (1.2% each).

Adverse reactions leading to dose interruption of intravenous pembrolizumab in the neoadjuvant phase occurred in 20% of patients. The most common adverse reactions (≥2%) leading to dose interruption of intravenous pembrolizumab were rash (4.8%) and neutropenia (2.4%). Of the 167 patients in the intravenous pembrolizumab in combination with enfortumab vedotin-ejfv arm who received neoadjuvant treatment, 7 (4.2%) patients did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery were acute myocardial infarction, bile duct cancer, colon cancer, respiratory distress, urinary tract infection, and the two deaths due to myasthenia gravis and toxic epidermal necrolysis (0.6% each).

Of the 146 patients who received neoadjuvant treatment with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv and underwent radical cystectomy, 6 (4.1%) patients experienced delay of

surgery (defined as time from last neoadjuvant treatment to surgery exceeding 8 weeks) due to adverse reactions.

Adjuvant Phase of KEYNOTE-905

Patients who did not proceed to surgery were ineligible for adjuvant therapy. Of the 146 patients who received neoadjuvant treatment and underwent surgery, 96 patients received adjuvant treatment with intravenous pembrolizumab with or without enfortumab vedotin-ejfv. Of the 50 patients who did not receive adjuvant intravenous pembrolizumab, discontinuation of intravenous pembrolizumab prior to the adjuvant phase was due to an adverse event in 19 patients.

In the adjuvant phase, serious adverse reactions occurred in 45% of patients who received intravenous pembrolizumab in the adjuvant phase; the most frequent (≥2%) serious adverse reactions were urinary tract infection (8%), acute kidney injury and pyelonephritis (5% each), urosepsis (4.2%), and hypokalemia, intestinal obstruction, and sepsis (2.1% each). Fatal adverse reactions occurred in 7% of patients who received intravenous pembrolizumab in the adjuvant phase, including urosepsis, intracranial hemorrhage, death, myocardial infarction, multiple organ dysfunction syndrome, and pseudomonal pneumonia (1% each).

Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 29% of patients who received intravenous pembrolizumab in the adjuvant phase. The most frequent (>2%) adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were diarrhea (5%), and peripheral neuropathy, acute kidney injury, and pneumonitis (2% each).

Adverse reactions leading to dose interruption of intravenous pembrolizumab in the adjuvant phase occurred in 40% of patients who received intravenous pembrolizumab in the adjuvant phase. The most common adverse reactions (≥2%) leading to dose interruption of intravenous pembrolizumab were rash (7%), urinary tract infection (6%), diarrhea (4%), and abdominal pain, COVID-19, fatigue, pruritus, and pyelonephritis (2% each).

BCG-unresponsive High-risk NMIBC

The safety of intravenous pembrolizumab was investigated in KEYNOTE-057, a multicenter, open-label, single-arm trial that enrolled 148 patients with high-risk non-muscle invasive bladder cancer (NMIBC), 96 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumors. Patients received intravenous pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

The median duration of exposure to intravenous pembrolizumab was 4.3 months (range: 1 day to 25.6 months).

Intravenous pembrolizumab was discontinued due to adverse reactions in 11% of patients. The most common adverse (>1%) reaction resulting in permanent discontinuation of intravenous pembrolizumab was pneumonitis (1.4%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 22% of patients; the most common (≥2%) were diarrhea (4%) and urinary tract infection (2%). Serious adverse reactions occurred in 28% of intravenous pembrolizumab-treated patients. The most frequent serious adverse reactions (≥2%) in intravenous pembrolizumab-treated patients were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). Tables 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-057.

Table 33: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-057

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks N=148	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	29	0.7
Peripheral edema‡	11	0
Gastrointestinal		
Diarrhea§	24	2.0
Nausea	13	0
Constipation	12	0
Skin and Subcutaneous Tissue		
Rash¶	24	0.7
Pruritus	19	0.7
Musculoskeletal and Connective Tissue		
Musculoskeletal pain#	19	0
Arthralgia	14	1.4
Renal and Urinary		
Hematuria	19	1.4
Respiratory, Thoracic, and Mediastinal		
Cough Þ	19	0
Infections		
Urinary tract infection	12	2.0
Nasopharyngitis	10	0
Endocrine		
Hypothyroidism	11	0

* Graded per NCI CTCAE v4.03
† Includes asthenia, fatigue, malaise
‡ Includes edema peripheral, peripheral swelling
§ Includes diarrhea, gastroenteritis, colitis
¶ Includes rash maculo-papular, rash, rash erythematous, rash pruritic, rash pustular, erythema, eczema, eczema asteatotic, lichenoid keratosis, urticaria, dermatitis
# Includes back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, neck pain
Þ Includes cough, productive cough

Table 34: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of BCG-unresponsive NMIBC Patients Receiving Intravenous Pembrolizumab in KEYNOTE-057

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	59	7
Increased ALT	25	2.7
Hyponatremia	24	7
Hypophosphatemia	24	6
Hypoalbuminemia	24	1.4
Hyperkalemia	23	1.4
Hypocalcemia	22	0.7
Increased AST	20	2.7
Increased creatinine	20	0.7
Hematology		
Anemia	35	1.4
Lymphopenia	29	1.6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 124 to 147 patients)
† Graded per NCI CTCAE v4.03

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The safety of intravenous pembrolizumab was investigated in 504 patients with MSI-H or dMMR cancer enrolled in KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 *[see Clinical Studies (14.8)].* The median duration of exposure to intravenous pembrolizumab was 6.2 months (range: 1 day to 53.5 months). Adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with other solid tumors who received intravenous pembrolizumab as a single agent.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

Among the 153 patients with MSI-H or dMMR CRC enrolled in KEYNOTE-177 *[see Clinical Studies (14.9)]* treated with intravenous pembrolizumab, the median duration of exposure to intravenous pembrolizumab was 11.1 months (range: 1 day to 30.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent.

Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma

The safety of intravenous pembrolizumab was evaluated in 696 patients with HER2-positive gastric or GEJ cancer enrolled in KEYNOTE-811, which included 350 patients treated with intravenous pembrolizumab 200 mg, trastuzumab, and CAPOX (n=297) or FP (n=53) every 3 weeks, compared to 346 patients treated with placebo, trastuzumab, and CAPOX (n=298) or FP (n=48) every 3 weeks *[see Clinical Studies (14.10)]*.

The median duration of exposure to intravenous pembrolizumab was 9.2 months (range: 1 day to 33.6 months).

Fatal adverse reactions occurred in 3 patients who received intravenous pembrolizumab in combination with trastuzumab and CAPOX or FP and included pneumonitis in 2 patients and hepatitis in 1 patient.

Intravenous pembrolizumab was discontinued due to adverse reactions in 13% of patients. Adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab in ≥1% of patients were pneumonitis (2.0%) and pneumonia (1.1%).

Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 71% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhea (7%), pneumonia (5%), anemia (4.9%), COVID-19 (3.1%), hypokalemia (3.1%), fatigue/asthenia (4.9%), decreased appetite (4%), increased AST (3.7%), increased blood bilirubin (4.6%), increased ALT (2.9%), vomiting (2.6%), pneumonitis (2.3%), pyrexia (2.3%), increased blood creatinine (2%), and colitis (2%).

In the intravenous pembrolizumab arm versus placebo, there was a difference of ≥5% incidence between patients treated with intravenous pembrolizumab versus standard of care for diarrhea (53% vs. 47%), rash (35% vs. 28%), hypothyroidism (11% vs. 5%), and pneumonia (11% vs. 5%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of ≥5% incidence between patients treated with intravenous pembrolizumab versus standard of care for decreased leukocytes (60% vs. 54%), decreased calcium (56% vs. 46%), decreased lymphocytes (59% vs. 51%), decreased potassium (41% vs. 36%), increased bilirubin (33% vs. 25%), increased creatinine (28% vs. 18%), and decreased glucose (17% vs. 11%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma

The safety of intravenous pembrolizumab was evaluated in 1572 patients with HER2-negative gastric or GEJ cancer enrolled in KEYNOTE-859, which included 785 patients treated with intravenous pembrolizumab 200 mg and FP (n=106) or CAPOX (n=674) every 3 weeks, compared to 787 patients who received placebo and FP (n=107) or CAPOX (n=679) every 3 weeks *[see Clinical Studies (14.10)]*.

The median duration of exposure to intravenous pembrolizumab was 6.2 months (range: 1 day to 33.7 months).

Serious adverse reactions occurred in 45% of patients receiving intravenous pembrolizumab. Serious adverse reactions in >2% of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%). Fatal adverse reactions occurred in 8% of patients who received intravenous pembrolizumab, including infection (2.3%) and thromboembolism (1.3%).

Permanent discontinuation of intravenous pembrolizumab due to adverse reactions occurred in 15% of patients. Adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab in ≥1% were infections (1.8%) and diarrhea (1.0%).

Dosage interruptions of intravenous pembrolizumab due to an adverse reaction occurred in 65% of patients. Adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhea (5.5%), fatigue (4.8%), infection (4.8%), anemia (4.5%), increased AST (4.3%), increased ALT (3.8%), increased blood bilirubin (3.3%), white blood cell count decreased (2.2%), nausea (2%), palmar-plantar erythrodysesthesia syndrome (2%), and vomiting (2%).

Tables 35 and 36 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-859.

Table 35: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-859

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks and FP or CAPOX n=785		Placebo and FP or CAPOX n=787	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy†	47	5	48	6
Gastrointestinal				
Nausea	46	3.7	46	4.4
Diarrhea	36	6	32	5
Vomiting	34	5	27	5
Abdominal Pain‡	26	2.8	24	2.9
Constipation	22	0.5	21	0.8
General				
Fatigue§	40	8	39	9
Metabolism and Nutrition				
Decreased appetite	29	3.3	29	2.5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	25	3.1	22	1.8
Investigations				
Weight loss	20	2.8	19	2.7

* Graded per NCI CTCAE v4.03

† Includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy

‡ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, abdominal pain upper, epigastric discomfort, gastrointestinal pain

§ Includes asthenia, fatigue

Table 36: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-859

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks and FP or CAPOX		Placebo and FP or CAPOX	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	65	15	69	13
Thrombocytopenia	64	12	62	10
Neutropenia	63	25	58	20
Leukopenia	59	7	56	6
Lymphopenia	57	20	51	16
Chemistry				
Increased AST	57	4.7	48	3.6
Hypoalbuminemia	55	4.1	52	2.9
Hyperglycemia	53	6	52	4.6
Hypocalcemia	49	3.6	45	3.3
Increased alkaline phosphatase	48	6	41	5
Hyponatremia	40	13	40	12
Increased ALT	40	4.2	29	2.9
Hypokalemia	35	10	27	9
Bilirubin increased	32	5	30	5
Hypophosphatemia	30	10	27	8
Hypomagnesemia	29	0.3	22	0.7
Increased creatinine	21	3.5	18	1.7
Hyperkalemia	20	3.7	18	2.9
Increased INR	20	1.4	22	0

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab/FP or CAPOX (range: 210 to 766 patients) and placebo/FP or CAPOX (range: 190 to 762 patients)

† Graded per NCI CTCAE v4.03

Esophageal Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal Cancer/Gastroesophageal Junction

The safety of intravenous pembrolizumab, in combination with cisplatin and FU chemotherapy was investigated in KEYNOTE-590, a multicenter, double-blind, randomized (1:1), placebo-controlled trial for the first-line treatment in patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.11)]*. A total of 740 patients received either intravenous pembrolizumab 200 mg (n=370) or placebo (n=370) every 3 weeks for up to 35 cycles, both in combination with up to 6 cycles of cisplatin and up to 35 cycles of FU.

The median duration of exposure was 5.7 months (range: 1 day to 26 months) in the intravenous pembrolizumab combination arm and 5.1 months (range: 3 days to 27 months) in the chemotherapy arm.

Intravenous pembrolizumab was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 67% of patients. The most common adverse reactions leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

Tables 37 and 38 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-590.

Table 37: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-590

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks Cisplatin FU n=370		Placebo Cisplatin FU n=370	
	All Grades* (%)	Grades 3-4† (%)	All Grades* (%)	Grades 3-4† (%)
Gastrointestinal				
Nausea	67	7	63	7
Constipation	40	0	40	0
Diarrhea	36	4.1	33	3
Vomiting	34	7	32	5
Stomatitis	27	6	26	3.8
General				
Fatigue‡	57	12	46	9
Metabolism and Nutrition				
Decreased appetite	44	4.1	38	5
Investigations				
Weight loss	24	3.0	24	5

* Graded per NCI CTCAE v4.03
† One fatal event of diarrhea was reported in each arm.
‡ Includes asthenia, fatigue

Table 38: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Esophageal Cancer Patients Receiving Intravenous Pembrolizumab in KEYNOTE-590

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks Cisplatin FU		Chemotherapy (Cisplatin and FU)	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	84	21	87	25
Neutropenia	77	44	73	41
Leukopenia	73	21	73	17
Lymphopenia	57	23	53	18
Thrombocytopenia	43	5	46	8
Chemistry				
Hyperglycemia	56	7	55	6
Hyponatremia	53	19	53	19
Hypoalbuminemia	53	2.8	52	2.3
Increased creatinine	45	2.5	42	2.5
Hypocalcemia	44	3.9	37	2
Hypophosphatemia	37	9	31	10
Hypokalemia	30	12	34	15
Increased alkaline phosphatase	29	1.9	29	1.7
Hyperkalemia	28	3.6	28	2.5
Increased AST	25	4.4	22	2.8
Increased ALT	23	3.6	18	1.7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab/cisplatin/FU (range: 353 to 365 patients) and placebo/cisplatin/FU (range: 347 to 359 patients)
† Graded per NCI CTCAE v4.03

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 *[see Clinical Studies (14.11)]* treated with intravenous pembrolizumab, the median duration of exposure to intravenous pembrolizumab was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition

that required immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent.

Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The safety of intravenous pembrolizumab in combination with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18, a placebo-controlled, randomized (1:1), multicenter, double-blind trial including 597 patients with FIGO 2014 Stage III-IVA cervical cancer *[see Clinical Studies (14.12)]*. Two hundred ninety-four patients received intravenous pembrolizumab in combination with chemoradiotherapy and 303 patients received placebo in combination with chemoradiotherapy.

The median duration of exposure to intravenous pembrolizumab was 20 months (range: 1 day to 32 months).

Fatal adverse reactions occurred in 1.4% of patients receiving intravenous pembrolizumab in combination with chemoradiotherapy, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage.

Serious adverse reactions occurred in 34% of patients receiving intravenous pembrolizumab in combination with chemoradiotherapy. Serious adverse reactions occurring in ≥1% of patients included urinary tract infection (3.1%), urosepsis (1.4%), and sepsis (1%).

Intravenous pembrolizumab was discontinued for adverse reactions in 9% of patients. The most common adverse reaction (≥1%) resulting in permanent discontinuation was diarrhea (1%).

Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 47% of patients; the most common adverse reactions leading to interruption of intravenous pembrolizumab (≥2%) were anemia (7%), COVID-19 (7%), SARS-CoV-2 test positive (4.8%), diarrhea (4.1%), increased ALT (4.1%), increased AST (3.4%) decreased neutrophil count (3.1%), and urinary tract infection (2.7%).

Table 39 and Table 40 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-A18.

Table 39: Adverse Reactions Occurring in ≥10% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving Intravenous Pembrolizumab in KEYNOTE-A18

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy n=294		Placebo with chemoradiotherapy n=303	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	0	62	2.3
Diarrhea	51	4.4	50	4.3
Vomiting	34	1.0	35	1.7
Constipation	20	0	19	0.7
Abdominal pain	13	1.0	14	1.7
Infections				
Urinary tract infection†	35	4.8	34	5
COVID-19	10	0	7	1.0
General				
Fatigue‡	28	1.0	28	1.3
Pyrexia	14	0.7	15	0
Endocrine				
Hypothyroidism§	23	0.7	8	0
Hyperthyroidism	13	0.3	3.3	0
Investigations				

Weight loss	19	2.4	19	1.0
Metabolism and Nutrition				
Decreased appetite	18	0.7	17	0.3
Renal and Urinary				
Dysuria	12	0.3	12	0
Skin and Subcutaneous Tissue Disorders				
Rash¶	12	1.0	8	0.3
Musculoskeletal and Connective Tissues Disorders				
Back pain	11	0.7	11	0.7
Reproductive System				
Pelvic pain	11	1.0	14	1.7

* Graded per NCI CTCAE v5.0
† Includes urinary tract infection, urinary tract infection pseudomonal, pyelonephritis acute, cystitis, Escherichia urinary tract infection
‡ Includes fatigue, asthenia
§ Includes hypothyroidism, autoimmune hypothyroidism
¶ Includes erythema multiforme, dermatitis, drug eruption, eczema, rash, skin exfoliation, dermatitis bullous, rash maculo-papular, lichen planus, dyshidrotic eczema, dermatitis acneiform

Table 40: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving Intravenous Pembrolizumab in KEYNOTE-A18

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy		Placebo with chemoradiotherapy	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	99	96	99	92
Leukopenia	96	48	94	49
Anemia	87	33	82	27
Neutropenia	76	33	76	33
Thrombocytopenia	64	9	62	7
Chemistry				
Hypomagnesemia	61	4.2	63	3.7
Hyponatremia	56	4.8	50	4.7
Increased AST	50	1.7	44	2.3
Increased ALT	49	3.1	46	1
Hypocalcemia	45	5	43	5
Hypokalemia	44	15	41	11
Increased creatinine	44	7	46	6
Hypoalbuminemia	38	2.4	37	2.3
Increased alkaline phosphatase	38	0.3	35	0.3
Hyperkalemia	21	2.0	16	1

* Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: Intravenous pembrolizumab + chemoradiotherapy (range: 288 to 293 patients) and placebo + chemoradiotherapy (range: 299 to 301 patients)
† Graded per NCI CTCAE v5.0

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of intravenous pembrolizumab in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent *[see Clinical Studies (14.12)]*. A total of 616 patients, regardless of tumor PD-L1

expression, received intravenous pembrolizumab 200 mg and chemotherapy with or without bevacizumab (n=307) every 3 weeks or placebo and chemotherapy with or without bevacizumab (n=309) every 3 weeks.

The median duration of exposure to intravenous pembrolizumab was 9.9 months (range: 1 day to 26 months).

Fatal adverse reactions occurred in 4.6% of patients receiving intravenous pembrolizumab in combination with chemotherapy with or without bevacizumab, including 3 cases of hemorrhage, 2 cases of sepsis, 2 cases due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection.

Serious adverse reactions occurred in 50% of patients receiving intravenous pembrolizumab in combination with chemotherapy with or without bevacizumab. Serious adverse reactions in ≥3% of patients included febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), acute kidney injury (3.3%), and sepsis (3.3%).

Intravenous pembrolizumab was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) was colitis (1%).

Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 66% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were thrombocytopenia (15%), neutropenia (14%), anemia (11%), increased ALT (6%), leukopenia (5%), fatigue/asthenia (4.2%), urinary tract infection (3.6%), increased AST (3.3%), pyrexia (3.3%), diarrhea (2.6%), acute kidney injury (2.6%), increased blood creatinine (2.6%), colitis (2.3%), decreased appetite (2%), and cough (2%).

For patients treated with intravenous pembrolizumab, chemotherapy, and bevacizumab (n=196), the most common (≥20%) adverse reactions were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea (41%), neutropenia (41%), diarrhea (39%), hypertension (35%), thrombocytopenia (35%), constipation (31%), arthralgia (31%), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

Table 41 and Table 42 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-826.

Table 41: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-826

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=307		Placebo and chemotherapy* with or without bevacizumab n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy‡	58	4.2	57	6
Skin and Subcutaneous Tissue				
Alopecia	56	0	58	0
Rash§	22	3.6	15	0.3
General				
Fatigue¶	47	7	46	6
Gastrointestinal				
Nausea	40	2	44	1.6
Diarrhea	36	2	30	2.6
Constipation	28	0.3	33	1
Vomiting	26	2.6	27	1.9
Musculoskeletal and Connective Tissue				
Arthralgia	27	0.7	26	1.3
Vascular				
Hypertension	24	9	23	11

Infections				
Urinary tract infection	24	9	26	8

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Graded per NCI CTCAE v4.0
‡ Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia
§ Includes rash, rash maculo-papular, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular
¶ Includes fatigue, asthenia

Table 42: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-826

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks and chemotherapy† with or without bevacizumab n=307		Placebo and chemotherapy† with or without bevacizumab n=309	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades‡ (%)	Grades 3-4 (%)
Hematology				
Anemia	80	35	77	33
Leukopenia	76	27	69	19
Neutropenia	73	43	62	32
Lymphopenia	64	35	59	35
Thrombocytopenia	57	19	53	15
Chemistry				
Hyperglycemia	51	4.7	46	2.3
Hypoalbuminemia	46	1.4	37	5
Hyponatremia	39	14	38	11
Increased ALT	40	7	38	6
Increased AST	40	6	36	3.0
Increased alkaline phosphatase	38	3.4	40	2.3
Hypocalcemia	37	4.1	31	5
Increased creatinine	34	5	32	6
Hypokalemia	29	7	26	7
Hyperkalemia	23	3.7	27	4.7
Hypercalcemia	21	1.0	20	1.3

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab plus chemotherapy (range: 296 to 301 patients) and placebo plus chemotherapy (range: 299 to 302 patients)
† Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
‡ Graded per NCI CTCAE v4.0

Previously Treated Recurrent or Metastatic Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of KEYNOTE-158 *[see Clinical Studies (14.12)]*, the median duration of exposure to intravenous pembrolizumab was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Intravenous pembrolizumab was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving intravenous pembrolizumab. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 43 and 44 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-158.

Table 43: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks N=98	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	43	5
Pain‡	22	2.0
Pyrexia	19	1.0
Edema peripheral§	15	2.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain¶	27	5
Gastrointestinal		
Diarrhea#	23	2.0
Abdominal painÞ	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhageß	19	5
Infections		
UTIà	18	6
Infection (except UTI)è	16	4.1
Skin and Subcutaneous Tissue		
Rashð	17	2.0
Endocrine		
Hypothyroidism	11	0
Nervous System		
Headache	11	2.0
Respiratory, Thoracic and Mediastinal		
Dyspnea	10	1.0

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

‡ Includes breast pain, cancer pain, dysesthesia, dysuria, ear pain, gingival pain, groin pain, lymph node pain, oropharyngeal pain, pain, pain of skin, pelvic pain, radicular pain, stoma site pain, toothache

§ Includes edema peripheral, peripheral swelling

¶ Includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, myositis, neck pain, non-cardiac chest pain, pain in extremity

Includes colitis, diarrhea, gastroenteritis

Þ Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper

ß Includes epistaxis, hematuria, hemoptysis, metrorrhagia, rectal hemorrhage, uterine hemorrhage, vaginal hemorrhage

à Includes bacterial pyelonephritis, pyelonephritis acute, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis

è Includes cellulitis, clostridium difficile infection, device-related infection, empyema, erysipelas, herpes virus infection, infected neoplasm, infection, influenza, lower respiratory tract congestion, lung infection, oral candidiasis, oral fungal infection, osteomyelitis, pseudomonas infection, respiratory tract infection, tooth abscess, upper respiratory tract infection, uterine abscess, vulvovaginal candidiasis

ð Includes dermatitis, drug eruption, eczema, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash generalized, rash maculo-papular

Table 44: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	54	24
Lymphopenia	45	9
Chemistry		
Hypoalbuminemia	44	5
Increased alkaline phosphatase	40	1.3
Hyponatremia	38	13
Hyperglycemia	38	1.3
Increased AST	34	3.9
Increased creatinine	32	5
Hypocalcemia	27	0
Increased ALT	21	3.9
Hypokalemia	20	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 76 to 79 patients)

† Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥10% of patients receiving intravenous pembrolizumab were hypophosphatemia (19% all Grades; 6% Grades 3-4), increased INR (17% all Grades; 0% Grades 3-4), hypercalcemia (14% all Grades; 2.6% Grades 3-4), platelet count decreased (14% all Grades; 1.3% Grades 3-4), activated partial thromboplastin time prolonged (10% all Grades; 0% Grades 3-4), hypoglycemia (13% all Grades; 1.3% Grades 3-4), white blood cell decreased (13% all Grades; 2.6% Grades 3-4), and hyperkalemia (13% all Grades; 1.3% Grades 3-4).

HCC

Previously Treated HCC

The safety of intravenous pembrolizumab was investigated in KEYNOTE-394, a multicenter, double-blind, randomized, placebo-controlled trial that enrolled patients with previously treated HCC. Patients were randomized (2:1) and received intravenous pembrolizumab 200 mg (n=299) or placebo (n=153) intravenously every 3 weeks for up to 35 cycles *[see Clinical Studies (14.13)]*.

The median duration of exposure was 3.3 months (range: 1 day to 27.3 months) in the intravenous pembrolizumab arm and 2.2 months (range: 1 day to 15.5 months) in the placebo arm. Intravenous pembrolizumab was discontinued due to adverse reactions in 13% of patients. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab was ascites (2.3%). Adverse reactions leading to interruption of intravenous pembrolizumab occurred in 26% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were increased blood bilirubin (9%), increased AST (5%), and increased ALT (2%).

Tables 45 and 46 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-394.

Table 45: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving Intravenous Pembrolizumab in KEYNOTE-394

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks n=299		Placebo n=153	
	All Grades* (%)	Grades 3-5 (%)	All Grades* (%)	Grades 3-5 (%)
General				
Pyrexia	18	0.7	14	0
Skin and Subcutaneous Tissue				
Rash†	18	0.7	7	0
Pruritus	12	0	4	0
Gastrointestinal				
Diarrhea	16	1.7	9	0
Metabolism and Nutrition				
Decreased appetite	15	0.3	9	0
Infections				
Upper respiratory tract infection	11	1.0	7	0.7
Respiratory, Thoracic, and Mediastinal				
Cough	11	0	9	0
Endocrine				
Hypothyroidism	10	0	7	0

* Graded per NCI CTCAE v4.03

† Includes dermatitis, dermatitis allergic, dermatitis bullous, rash, rash erythematous, rash maculo-papular, rash pustular, and blister.

Table 46: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with HCC Receiving Intravenous Pembrolizumab in KEYNOTE-394

Laboratory Test*	Intravenous Pembrolizumab		Placebo	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased AST	54	14	44	12
Increased bilirubin	47	11	36	7
Increased ALT	47	7	32	4.6
Increased gamma-glutamyl transferase (GGT)	40	20	39	15
Hypoalbuminemia	40	0.7	20	0.7
Increased alkaline phosphatase	39	4.1	34	4
Hyperglycemia	36	3.3	26	1.4
Hyponatremia	36	11	28	5
Hypophosphatemia	30	6	17	4
Hypocalcemia	24	1.4	15	0.7
Hematology				
Lymphopenia	44	11	34	4.6
Anemia	36	7	30	3.3
Decreased platelets	32	4.7	29	2
Leukopenia	30	1.3	21	0.7
Neutropenia	25	4.4	21	2

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 223 to 297 patients) and placebo (range: 144 to 151 patients).

† Graded per NCI CTCAE v4.03

BTC

The safety of intravenous pembrolizumab in combination with gemcitabine and cisplatin, was investigated in KEYNOTE-966, a multicenter, double-blind, randomized, placebo-controlled trial in patients with locally advanced unresectable or metastatic BTC who had not received prior systemic therapy in the advanced disease setting *[see Clinical Studies (14.14)]*. A total of 1063 patients received either intravenous

pembrolizumab 200 mg plus gemcitabine and cisplatin chemotherapy (n=529) or placebo plus gemcitabine and cisplatin chemotherapy (n=534) every 3 weeks.

The median duration of exposure to intravenous pembrolizumab was 6 months (range: 1 day to 28 months).

Intravenous pembrolizumab was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) was pneumonitis (1.3%).

Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In the intravenous pembrolizumab plus chemotherapy versus placebo plus chemotherapy arms, there was a difference of ≥5% incidence in adverse reactions between patients treated with intravenous pembrolizumab versus placebo for pyrexia (26% vs. 20%), rash (21% vs. 13%), pruritus (15% vs. 10%), and hypothyroidism (9% vs. 2.6%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of ≥5% incidence in laboratory abnormalities between patients treated with intravenous pembrolizumab plus chemotherapy versus placebo plus chemotherapy for decreased lymphocytes (69% vs. 61%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

MCC

Among the 105 patients with MCC enrolled in KEYNOTE-017 and KEYNOTE-913 *[see Clinical Studies (14.15)]*, the median duration of exposure to intravenous pembrolizumab was 6.3 months (range: 1 day to 28 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included increased lipase (17%).

RCC

In combination with axitinib in the first-line treatment of advanced RCC (KEYNOTE-426)

The safety of intravenous pembrolizumab in combination with axitinib was investigated in KEYNOTE-426 *[see Clinical Studies (14.16)]*. Patients with medical conditions that required systemic corticosteroids or other immunosuppressive medications or had a history of severe autoimmune disease other than type 1 diabetes, vitiligo, Sjogren's syndrome, and hypothyroidism stable on hormone replacement were ineligible. Patients received intravenous pembrolizumab 200 mg intravenously every 3 weeks and axitinib 5 mg orally twice daily, or sunitinib 50 mg once daily for 4 weeks and then off treatment for 2 weeks. The median duration of exposure to the combination therapy of intravenous pembrolizumab and axitinib was 10.4 months (range: 1 day to 21.2 months).

The study population characteristics were: median age of 62 years (range: 30 to 89), 40% age 65 or older; 71% male; 80% White; and 80% Karnofsky Performance Status (KPS) of 90-100 and 20% KPS of 70-80.

Fatal adverse reactions occurred in 3.3% of patients receiving intravenous pembrolizumab in combination with axitinib. These included 3 cases of cardiac arrest, 2 cases of pulmonary embolism and 1 case each of cardiac failure, death due to unknown cause, myasthenia gravis, myocarditis, Fournier's gangrene, plasma cell myeloma, pleural effusion, pneumonitis, and respiratory failure.

Serious adverse reactions occurred in 40% of patients receiving intravenous pembrolizumab in combination with axitinib. Serious adverse reactions in ≥1% of patients receiving intravenous

pembrolizumab in combination with axitinib included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%).

Permanent discontinuation due to an adverse reaction of either intravenous pembrolizumab or axitinib occurred in 31% of patients; 13% intravenous pembrolizumab only, 13% axitinib only, and 8% both drugs. The most common adverse reaction (>1%) resulting in permanent discontinuation of intravenous pembrolizumab, axitinib, or the combination was hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of intravenous pembrolizumab infusions due to infusion-related reactions, occurred in 76% of patients receiving intravenous pembrolizumab in combination with axitinib. This includes interruption of intravenous pembrolizumab in 50% of patients. Axitinib was interrupted in 64% of patients and dose reduced in 22% of patients. The most common adverse reactions (>10%) resulting in interruption of intravenous pembrolizumab were hepatotoxicity (14%) and diarrhea (11%), and the most common adverse reactions (>10%) resulting in either interruption or reduction of axitinib were hepatotoxicity (21%), diarrhea (19%), and hypertension (18%).

The most common adverse reactions (≥20%) in patients receiving intravenous pembrolizumab and axitinib were diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.

Twenty-seven percent (27%) of patients treated with intravenous pembrolizumab in combination with axitinib received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 47 and 48 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with intravenous pembrolizumab and axitinib in KEYNOTE-426.

Table 47: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab with Axitinib in KEYNOTE-426

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks and Axitinib n=429		Sunitinib n=425	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, enteritis, enterocolitis hemorrhagic

‡ Includes hypertension, blood pressure increased, hypertensive crisis, labile hypertension

§ Includes ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased

¶ Includes rash, butterfly rash, dermatitis, dermatitis acneform, dermatitis atopic, dermatitis bullous, dermatitis contact, exfoliative rash, genital rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, seborrheic dermatitis, skin discoloration, skin exfoliation, perineal rash

Table 48: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab with Axitinib in KEYNOTE-426

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Hematology				
Lymphopenia	33	11	47	9
Anemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab/axitinib (range: 342 to 425 patients) and sunitinib (range: 345 to 421 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

In combination with lenvatinib in the first-line treatment of advanced RCC (KEYNOTE-581)

The safety of intravenous pembrolizumab was evaluated in KEYNOTE-581 *[see Clinical Studies (14.16)]*. Patients received intravenous pembrolizumab 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=352), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of intravenous pembrolizumab and lenvatinib was 17 months (range: 0.1 to 39).

Fatal adverse reactions occurred in 4.3% of patients treated with intravenous pembrolizumab in combination with lenvatinib, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving intravenous pembrolizumab and lenvatinib. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of either of intravenous pembrolizumab, lenvatinib or both due to an adverse reaction occurred in 37% of patients receiving intravenous pembrolizumab in combination with lenvatinib; 29% intravenous pembrolizumab only, 26% lenvatinib only, and 13% both. The most common adverse reactions (≥2%) resulting in permanent discontinuation of intravenous pembrolizumab, lenvatinib, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of intravenous pembrolizumab, lenvatinib, or both due to an adverse reaction occurred in 78% of patients receiving intravenous pembrolizumab in combination with lenvatinib. Intravenous pembrolizumab was interrupted in 55% of patients and both drugs were interrupted in 39% of patients. The most common adverse reactions (≥3%) resulting in interruption of intravenous pembrolizumab were diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%).

Fifteen percent (15%) of patients treated with intravenous pembrolizumab in combination with lenvatinib received an oral prednisone equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 49 and 50 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in ≥20% of patients treated with intravenous pembrolizumab and lenvatinib in KEYNOTE-581.

Table 49: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab with Lenvatinib in KEYNOTE-581

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks with Lenvatinib N=352		Sunitinib 50 mg N=340	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue*	63	9	56	8
Gastrointestinal				
Diarrhea†	62	10	50	6
Stomatitis‡	43	2	43	2
Nausea	36	3	33	1
Abdominal pain§	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders¶	58	4	41	3
Endocrine				
Hypothyroidism#	57	1	32	0
Vascular				
Hypertensionᵇ	56	29	43	20
Hemorrhagic eventsß	27	5	26	4
Metabolism				
Decreased appetiteª	41	4	31	1
Skin and Subcutaneous Tissue				
Rashᵉ	37	5	17	1
Palmar-plantar erythrodysesthesia syndromeδ	29	4	38	4
Investigations				
Weight loss	30	8	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	30	0	4	0
Renal and Urinary				
Proteinuriaø	30	8	13	3
Acute kidney injuryý	21	5	16	2
Hepatobiliary				
Hepatotoxicity£	25	9	21	5
Nervous System				
Headache	23	1	16	1

* Includes asthenia, fatigue, lethargy, malaise

† Includes diarrhea, gastroenteritis

‡ Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis

§ Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, upper abdominal pain

¶ Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw

Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism

Þ Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure

ß Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, upper gastrointestinal hemorrhage

à Includes decreased appetite, early satiety

è Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular

ð Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema

ø Includes hemoglobinuria, nephrotic syndrome, proteinuria

ý Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic

£ Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, gamma-glutamyltransferase increased

Clinically relevant adverse reactions (<20%) that occurred in patients receiving intravenous pembrolizumab with lenvatinib were myocardial infarction (3%) and angina pectoris (1%).

Table 50: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) of Patients Receiving Intravenous Pembrolizumab with Lenvatinib in KEYNOTE-581

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks with Lenvatinib		Sunitinib 50 mg	
	All Grades %†	Grade 3-4 %†	All Grades %†	Grade 3-4 %†
Chemistry				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased AST	58	7	57	3
Hyperglycemia	55	7	48	3
Increased ALT	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Decreased albumin	34	0.3	22	0
Increased alkaline phosphatase	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16

* With at least one Grade increase from baseline

† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: intravenous pembrolizumab with lenvatinib (range: 343 to 349 patients) and sunitinib (range: 329 to 335 patients).

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed on rechallenge in 10 patients receiving both intravenous pembrolizumab and lenvatinib (n=38) and was not observed on rechallenge with intravenous pembrolizumab alone (n=3).

Adjuvant treatment of RCC (KEYNOTE-564)

The safety of intravenous pembrolizumab as a single agent was investigated in KEYNOTE-564, a randomized (1:1) double-blind placebo-controlled trial in which 984 patients who had undergone nephrectomy for RCC received 200 mg of intravenous pembrolizumab by intravenous infusion every 3 weeks (n=488) or placebo (n=496) for up to one year *[see Clinical Studies (14.16)]*. The median duration of exposure to intravenous pembrolizumab was 11.1 months (range: 1 day to 14.3 months). Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Serious adverse reactions occurred in 20% of these patients receiving intravenous pembrolizumab. Serious adverse reactions (≥1%) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% of those treated with intravenous pembrolizumab, including one case of pneumonia.

Discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 21% of patients; the most common (≥1%) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%).

Dose interruptions of intravenous pembrolizumab due to an adverse reaction occurred in 26% of patients; the most common (≥1%) were increased AST (2.3%), arthralgia (1.6%), hypothyroidism (1.6%), diarrhea (1.4%), increased ALT (1.4%), fatigue (1.4%), rash, decreased appetite, and vomiting (1% each).

Tables 51 and 52 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in KEYNOTE-564.

Table 51: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-564

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks n=488		Placebo n=496	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue				
Musculoskeletal pain‡	41	1.2	36	0.6
General				
Fatigue§	40	1.2	31	0.2
Skin and Subcutaneous Tissue				
Rash¶	30	1.4	15	0.4
Pruritus	23	0.2	13	0
Gastrointestinal				
Diarrhea#	27	2.7	23	0.2
Nausea	16	0.4	10	0
Abdominal painÞ	11	0.4	13	0.2
Endocrine				
Hypothyroidism	21	0.2	3.6	0
Hyperthyroidism	12	0.2	0.2	0
Respiratory, Thoracic and Mediastinal				
Coughß	17	0	12	0
Nervous System				
Headacheà	15	0.2	13	0
Hepatobiliary				
Hepatotoxicityè	14	3.7	7	0.6
Renal and Urinary				
Acute kidney injuryð	13	1.2	10	0.2

* Adverse reactions occurring at same or higher incidence than in placebo arm

† Graded per NCI CTCAE v4.0

‡ Includes arthralgia, back pain, myalgia, arthritis, pain in extremity, neck pain, musculoskeletal pain, musculoskeletal stiffness, spinal pain, musculoskeletal chest pain, bone pain, musculoskeletal discomfort

§ Includes asthenia, fatigue

¶ Includes rash, rash maculo-papular, rash papular, skin exfoliation, lichen planus, rash erythematous, eczema, rash macular, dermatitis acneiform, dermatitis, rash pruritic, Stevens-Johnson Syndrome, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome

\# Includes diarrhea, colitis, enterocolitis, frequent bowel movements, enteritis

Þ Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, gastrointestinal pain

ß Includes upper-airway cough syndrome, productive cough, cough

à Includes tension headache, headache, sinus headache, migraine with aura

è Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, transaminases increased, gamma-glutamyltransferase increased, bilirubin conjugated increased

ð Includes acute kidney injury, blood creatinine increased, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, nephropathy toxic

Table 52: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-564

Laboratory Test†	Intravenous Pembrolizumab 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	48	8	45	4.5
Increased creatinine	39	1.1	28	0.2
Increased INR	29	1.0	20	0.9
Hyponatremia	21	3.3	13	1.9
Increased ALT	20	3.6	11	0.2
Hematology				
Anemia	28	0.5	20	0.4

* Laboratory abnormalities occurring at same or higher incidence than placebo

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab (range: 440 to 449 patients) and placebo (range: 461 to 469 patients); increased INR: intravenous pembrolizumab n=199 and placebo n=224.

‡ Graded per NCI CTCAE v4.03

In combination with belzutifan for the adjuvant treatment of ccRCC (LITESPARK-022)

The safety of intravenous pembrolizumab in combination with belzutifan versus intravenous pembrolizumab in combination with placebo was investigated in LITESPARK-022, a randomized, double-blind trial in 1,828 patients who had undergone nephrectomy for ccRCC *[see Clinical Studies (14.16)]*. Patients received either intravenous pembrolizumab 400 mg every 6 weeks in combination with belzutifan 120 mg orally once daily (n=915) or intravenous pembrolizumab 400 mg every 6 weeks in combination with oral placebo (n=913) for up to 9 cycles (54 weeks) until disease recurrence or unacceptable toxicity. The median duration of exposure to intravenous pembrolizumab in the treatment arm was 11.1 months (range: 1 day to 16.1 months).

Serious adverse reactions occurred in 30% of patients who received intravenous pembrolizumab in combination with belzutifan. Serious adverse reactions in ≥1% of patients included pneumonia (2%), hypoxia (1.9%), pneumonitis (1.6%), arrhythmia (1.5%), diarrhea (1.1%), and acute kidney injury (1.1%). Fatal adverse reactions occurred in 1.1% of patients who received intravenous pembrolizumab in combination with belzutifan, including sepsis (0.1%).

Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 23% of patients. Adverse reactions which resulted in permanent discontinuation of intravenous pembrolizumab in ≥1% of patients included increased ALT (4.5%), increased AST (3%), pneumonitis (2.4%), diarrhea (2.4%), and rash (1.5%).

Dose interruptions of intravenous pembrolizumab due to an adverse reaction occurred in 29% of patients. Adverse reactions which required dosage interruption of intravenous pembrolizumab in ≥2% of patients included anemia (3.2%), diarrhea (3%), increased ALT (3%), and increased AST (2.5%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, in patients who received intravenous pembrolizumab in combination with belzutifan were decreased hemoglobin, increased ALT, fatigue, increased AST, decreased lymphocytes, and increased alkaline phosphatase.

Tables 53 and 54 summarize adverse reactions and laboratory abnormalities, respectively, in LITESPARK-022.

Table 53: Adverse Reactions (≥10%) of Patients with ccRCC Who Received Intravenous Pembrolizumab in Combination with Belzutifan [at a Higher Incidence (Between Arm Difference of ≥4%) Compared to Control] in LITESPARK-022

Adverse Reaction	Intravenous Pembrolizumab 400 mg every 6 weeks plus Belzutifan n=915		Intravenous Pembrolizumab 400 mg every 6 weeks plus Placebo n=913	
	All Grades* (%)	Grade 3-4 (%)	All Grades* (%)	Grade 3-4 (%)
General				
Fatigue†	49	3.1	33	0.7
Gastrointestinal				
Diarrhea†	23	3	18	2.4
Nausea	16	0.3	12	0.2
Nervous system				
Dizziness†	23	0.4	10	0.1
Headache	17	0.7	11	0.1
Respiratory, thoracic, and mediastinal				
Dyspnea†	12	0.9	6	0.1

* Graded per NCI CTCAE v5.0
† Includes other related terms

Table 54: Laboratory Abnormalities Worsened from Baseline (≥20%) in Patients with ccRCC Who Received Intravenous Pembrolizumab in Combination with Belzutifan [at a Higher Incidence (Between Arm Difference of ≥10%) Compared to Control] in LITESPARK-022

Laboratory Test*	Intravenous Pembrolizumab plus Belzutifan		Intravenous Pembrolizumab plus Placebo	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Decreased hemoglobin	95	11	26	0.7
Decreased lymphocytes	38	9	25	7
Chemistry				
Increased ALT	57	13	33	3.2
Increased AST	46	8	29	3.1
Increased alkaline phosphatase	29	2.3	18	0.4

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab + belzutifan (range: 907 to 911 patients), and intravenous pembrolizumab + placebo (range: 905 to 912 patients).
† Graded per NCI CTCAE v5.0

Endometrial Carcinoma

Primary Advanced or Recurrent Endometrial Carcinoma

The safety of intravenous pembrolizumab in combination with chemotherapy (paclitaxel and carboplatin) was investigated in KEYNOTE-868, a randomized (1:1), multicenter, double-blind, placebo-controlled trial that enrolled patients with advanced or recurrent endometrial carcinoma *[see Clinical Studies (14.17)]*. A total of 759 patients received intravenous pembrolizumab 200 mg every 3 weeks and chemotherapy for 6 cycles followed by intravenous pembrolizumab 400 mg every 6 weeks for up to 14 cycles (n=382) or

placebo and chemotherapy for 6 cycles followed by placebo for up to 14 cycles (n=377). The median duration of exposure to intravenous pembrolizumab was 5.6 months (range: 1 day to 24.0 months).

Serious adverse reactions occurred in 35% of patients receiving intravenous pembrolizumab in combination with chemotherapy, compared to 19% of patients receiving placebo in combination with chemotherapy.

Fatal adverse reactions occurred in 1.6% of patients receiving intravenous pembrolizumab in combination with chemotherapy, including COVID-19 (0.5%), and cardiac arrest (0.3%).

Intravenous pembrolizumab was discontinued for an adverse reaction in 14% of patients. Chemotherapy dose reduction was required in 29% of patients receiving intravenous pembrolizumab in combination with chemotherapy, compared to 23% of patients receiving placebo in combination with chemotherapy. There were no clinically meaningful differences in chemotherapy discontinuations or interruptions between arms.

Adverse reactions occurring in patients treated with intravenous pembrolizumab and chemotherapy were generally similar to those observed with intravenous pembrolizumab alone or chemotherapy alone with the exception of rash (33% all Grades; 2.9% Grades 3-4).

In Combination with Lenvatinib for the Treatment of Advanced Endometrial Carcinoma That Is pMMR or Not MSI-H.

The safety of intravenous pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings *[see Clinical Studies (14.17)].* Patients with endometrial carcinoma that is pMMR or not MSI-H received intravenous pembrolizumab 200 mg every 3 weeks in combination with lenvatinib 20mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

For patients with pMMR or not MSI-H tumor status, the median duration of study treatment was 7.2 months (range: 1 day to 26.8 months) and the median duration of exposure to intravenous pembrolizumab was 6.8 months (range: 1 day to 25.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with intravenous pembrolizumab and lenvatinib, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving intravenous pembrolizumab and lenvatinib. Serious adverse reactions (≥3%) were hypertension (4.4%) and urinary tract infections (3.2%).

Discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of intravenous pembrolizumab (≥1%) was increased ALT (1.2%).

Dose interruptions of intravenous pembrolizumab due to an adverse reaction occurred in 48% of these patients. The most common adverse reactions leading to interruption of intravenous pembrolizumab (≥3%) were diarrhea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Tables 55 and 56 summarize adverse reactions and laboratory abnormalities, respectively, in patients on intravenous pembrolizumab in combination with lenvatinib in KEYNOTE-775.

Table 55: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-775

Adverse Reaction	Endometrial Carcinoma (pMMR or not MSI-H)			
	Intravenous Pembrolizumab 200 mg every 3 weeks and Lenvatinib n=342		Doxorubicin or Paclitaxel n=325	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism[†]	67	0.9	0.9	0
Vascular				
Hypertension[‡]	67	39	6	2.5
Hemorrhagic events[§]	25	2.6	15	0.9
General				
Fatigue[¶]	58	11	54	6
Gastrointestinal				
Diarrhea[#]	55	8	20	2.8
Nausea	49	2.9	47	1.5
Vomiting	37	2.3	21	2.2
Stomatitis[Þ]	35	2.6	26	1.2
Abdominal pain[ß]	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders[à]	53	5	27	0.6
Metabolism				
Decreased appetite[è]	44	7	21	0
Investigations				
Weight loss	34	10	6	0.3
Renal and Urinary				
Proteinuria[ð]	29	6	3.4	0.3
Infections				
Urinary tract infection[ø]	31	5	13	1.2
Nervous System				
Headache	26	0.6	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	22	0	0.6	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia[ý]	23	2.9	0.9	0
Rash[£]	20	2.3	4.9	0

* Graded per NCI CTCAE v4.03

† Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, secondary hypothyroidism

‡ Includes hypertension, blood pressure increased, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, blood pressure fluctuation

§ Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, melena, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, vessel puncture site bruise

¶ Includes fatigue, asthenia, malaise, lethargy

Includes diarrhea, gastroenteritis

Þ Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration

ß Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort

à Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw

è Includes decreased appetite, early satiety

ð Includes proteinuria, protein urine present, hemoglobinuria

ø Includes urinary tract infection, cystitis, pyelonephritis

ý Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema

£ Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, application site rash

Table 56: Laboratory Abnormalities Worsened from Baseline* Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-775

	Endometrial Carcinoma (pMMR or not MSI-H)			
Laboratory Test†	**Intravenous Pembrolizumab 200 mg every 3 weeks and Lenvatinib**		**Doxorubicin or Paclitaxel**	
	All Grades‡ %	**Grades 3-4 %**	**All Grades‡ %**	**Grades 3-4 %**
Chemistry				
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased aspartate aminotransferase	58	9	23	1.6
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	46	0	27	1.3
Increased alanine aminotransferase	55	9	21	1.2
Hypercholesterolemia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased alkaline phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.9
Increased lipase	36	14	13	3.9
Increased creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased amylase	25	7	8	1
Hyperkalemia	23	2.4	12	1.2
Increased creatine kinase	19	3.7	7	0
Increased bilirubin	18	3.6	6	1.6
Hematology				
Lymphopenia	51	18	66	23
Thrombocytopenia	50	8	30	4.7
Anemia	49	8	84	14
Leukopenia	43	3.5	83	43
Neutropenia	34	8	80	60

* With at least one grade increase from baseline
† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: intravenous pembrolizumab and lenvatinib (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients).
‡ Graded per NCI CTCAE v4.03

As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

Among the 90 patients with MSI-H or dMMR endometrial carcinoma enrolled in KEYNOTE-158 *[see Clinical Studies (14.17)]* treated with intravenous pembrolizumab as a single agent, the median duration of exposure to intravenous pembrolizumab was 8.3 months (range: 1 day to 26.9 months). Adverse reactions occurring in patients with endometrial carcinoma were similar to those occurring in 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent.

TMB-H Cancer

The safety of intravenous pembrolizumab was investigated in 105 patients with TMB-H cancer enrolled in KEYNOTE-158 *[see Clinical Studies (14.18)].* The median duration of exposure to intravenous pembrolizumab was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients

with TMB-H cancer were similar to those occurring in patients with other solid tumors who received intravenous pembrolizumab as a single agent.

cSCC

Among the 159 patients with advanced cSCC (recurrent or metastatic or locally advanced disease) enrolled in KEYNOTE-629 *[see Clinical Studies (14.19)]*, the median duration of exposure to intravenous pembrolizumab was 6.9 months (range: 1 day to 28.9 months). Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. Adverse reactions occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with intravenous pembrolizumab as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included lymphopenia (10%) and decreased sodium (10%).

TNBC

Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The safety of intravenous pembrolizumab in combination with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with intravenous pembrolizumab as a single agent was investigated in KEYNOTE-522, a randomized (2:1), multicenter, double-blind, placebo-controlled trial in patients with newly diagnosed, previously untreated, high-risk early-stage TNBC.

A total of 778 patients on the intravenous pembrolizumab arm received at least 1 dose of intravenous pembrolizumab in combination with neoadjuvant chemotherapy followed by intravenous pembrolizumab as adjuvant treatment after surgery, compared to 389 patients who received at least 1 dose of placebo in combination with neoadjuvant chemotherapy followed by placebo as adjuvant treatment after surgery *[see Clinical Studies (14.20)].*

The median duration of exposure to intravenous pembrolizumab 200 mg every 3 weeks was 13.3 months (range: 1 day to 21.9 months).

Fatal adverse reactions occurred in 0.9% of patients receiving intravenous pembrolizumab, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction.

Serious adverse reactions occurred in 44% of patients receiving intravenous pembrolizumab. Serious adverse reactions in ≥2% of patients who received intravenous pembrolizumab included febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%).

Intravenous pembrolizumab was discontinued for adverse reactions in 20% of patients. The most common adverse reactions (≥1%) resulting in permanent discontinuation of intravenous pembrolizumab were increased ALT (2.7%), increased AST (1.5%), and rash (1%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 57% of patients. The most common adverse reactions leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (26%), thrombocytopenia (6%), increased ALT (6%), increased AST (3.7%), anemia (3.5%), rash (3.2%), febrile neutropenia (2.8%), leukopenia (2.8%), upper respiratory tract infection (2.6%), pyrexia (2.2%), and fatigue (2.1%).

Tables 57 and 58 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with intravenous pembrolizumab in KEYNOTE-522.

Table 57: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-522

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy*/ Intravenous Pembrolizumab n=778		Placebo with chemotherapy*/Placebo n=389	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	70	8	66	3.9
Pyrexia	28	1.3	19	0.3
Gastrointestinal				
Nausea	67	3.7	66	1.8
Constipation	42	0	39	0.3
Diarrhea	41	3.2	34	1.8
Stomatitis§	34	2.7	29	1
Vomiting	31	2.7	28	1.5
Abdominal pain¶	24	0.5	23	0.8
Skin and Subcutaneous Tissue				
Alopecia	61	0	58	0
Rash#	52	5	41	0.5
Nervous System				
Peripheral neuropathyÞ	41	3.3	42	2.3
Headache	30	0.5	29	1
Musculoskeletal and Connective Tissue				
Arthralgia	29	0.5	31	0.3
Myalgia	20	0.5	19	0
Respiratory, Thoracic and Mediastinal				
Coughß	26	0.1	24	0
Metabolism and Nutrition				
Decreased appetite	23	0.9	17	0.3
Psychiatric				
Insomnia	21	0.5	19	0

* Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

† Graded per NCI CTCAE v4.0

‡ Includes asthenia, fatigue

§ Includes aphthous ulcer, cheilitis, lip pain, lip ulceration, mouth ulceration, mucosal inflammation, oral mucosal eruption, oral pain, stomatitis, tongue blistering, tongue ulceration

¶ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness

Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, incision site rash, injection site rash, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash rubelliform, skin exfoliation, skin toxicity, toxic skin eruption, urticaria, vasculitic rash, viral rash

Þ Includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy

ß Includes cough, productive cough, upper-airway cough syndrome

Table 58: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab in KEYNOTE-522

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy†/Intravenous Pembrolizumab		Placebo with chemotherapy†/Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Hematology				
Anemia	97	22	96	19
Leukopenia	93	41	91	32
Neutropenia	88	62	89	62
Lymphopenia	79	28	74	22
Thrombocytopenia	57	10	56	8
Chemistry				
Increased ALT	70	9	67	3.9
Increased AST	65	6	56	1.5
Hyperglycemia	63	4.3	61	2.8
Increased alkaline phosphatase	37	1	35	0.5
Hyponatremia	35	9	25	4.6
Hypoalbuminemia	34	1.0	30	1.3
Hypocalcemia	31	2.2	28	3.1
Hypokalemia	31	6	22	2.8
Hypophosphatemia	20	6	15	4.2

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab in combination with chemotherapy followed by intravenous pembrolizumab as a single agent (range: 762 to 777 patients) and placebo in combination with chemotherapy followed by placebo (range: 381 to 389 patients).

† Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

‡ Graded per NCI CTCAE v4.0

Locally Advanced or Metastatic TNBC

The safety of intravenous pembrolizumab in combination with sacituzumab govitecan-hziy was evaluated in KEYNOTE-D19 in 221 patients with unresectable locally advanced or metastatic TNBC who had not been previously treated with systemic therapy for advanced disease and whose tumors express PD-L1, and who had received at least one dose of intravenous pembrolizumab 200 mg every 3 weeks in combination with sacituzumab govitecan-hziy *[see Clinical Studies (14.20)]*. The median duration of exposure to intravenous pembrolizumab was 8.5 months (range: 1 day to 26.8 months).

Fatal adverse reactions occurred in 3.2% of patients receiving intravenous pembrolizumab in combination with sacituzumab govitecan-hziy, including death due to unknown cause (0.9%), and completed suicide, neutropenic sepsis, sepsis, pneumonia, and pulmonary embolism (0.5% each).

Serious adverse reactions occurred in 38% of patients receiving intravenous pembrolizumab in combination with sacituzumab govitecan-hziy. Serious adverse reactions in ≥2% of patients were febrile neutropenia (7%), neutropenia (6%), diarrhea (5%), fatigue and pneumonia (2.3% each).

Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 9% of patients. The adverse reactions which resulted in permanent discontinuation of intravenous pembrolizumab most commonly (≥1%) were pneumonitis and rash (1.4% each).

Dosage interruptions of intravenous pembrolizumab due to adverse reactions occurred in 67% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia (36%), diarrhea (7%), upper respiratory tract infection (4.5%), anemia (4.1%), fatigue (4.1%), increased ALT (3.2%), cough (2.7%), leukopenia (2.7%), nausea (2.7%), pyrexia (2.7%), rash (2.7%), vomiting (2.7%), and COVID-19 (2.3%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, occurring in patients treated with intravenous pembrolizumab in combination with sacituzumab govitecan-hziy were decreased neutrophil count and decreased hemoglobin (86% each), decreased leukocyte count (84%), diarrhea (72%), nausea (68%), decreased lymphocyte count (61%), fatigue (58%), alopecia (52%) increased alkaline phosphatase and increased glucose (50% each), increased alanine aminotransferase (47%),

constipation (41%), increased aspartate aminotransferase (40%), rash (37%), decreased potassium (35%), increased lactate dehydrogenase (34%), vomiting (29%), abdominal pain, headache, and increased eosinophils (26% each), and decreased albumin (25%).

Locally Recurrent Unresectable or Metastatic TNBC

The safety of intravenous pembrolizumab in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a multicenter, double-blind, randomized (2:1), placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting *[see Clinical Studies (14.20)]*. A total of 596 patients (including 34 patients from a safety run-in) received intravenous pembrolizumab 200 mg every 3 weeks in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin.

The median duration of exposure to intravenous pembrolizumab was 5.7 months (range: 1 day to 33.0 months).

Fatal adverse reactions occurred in 2.5% of patients receiving intravenous pembrolizumab in combination with chemotherapy, including cardio-respiratory arrest (0.7%) and septic shock (0.3%).

Serious adverse reactions occurred in 30% of patients receiving intravenous pembrolizumab in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin. Serious adverse reactions in ≥2% of patients were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%).

Intravenous pembrolizumab was discontinued for adverse reactions in 11% of patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 50% of patients. The most common adverse reactions leading to interruption of intravenous pembrolizumab (≥2%) were neutropenia (22%), thrombocytopenia (14%), anemia (7%), increased ALT (6%), leukopenia (5%), increased AST (5%), decreased white blood cell count (3.9%), and diarrhea (2%).

Tables 59 and 60 summarize the adverse reactions and laboratory abnormalities in patients on intravenous pembrolizumab in KEYNOTE-355.

Table 59: Adverse Reactions Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab with Chemotherapy in KEYNOTE-355

Adverse Reaction	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy n=596		Placebo every 3 weeks with chemotherapy n=281	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General				
Fatigue†	48	5	49	4.3
Gastrointestinal				
Nausea	44	1.7	47	1.8
Diarrhea	28	1.8	23	1.8
Constipation	28	0.5	27	0.4
Vomiting	26	2.7	22	3.2
Skin and Subcutaneous Tissue				
Alopecia	34	0.8	35	1.1
Rash‡	26	2	16	0
Respiratory, Thoracic and Mediastinal				
Cough§	23	0	20	0.4
Metabolism and Nutrition				
Decreased appetite	21	0.8	14	0.4
Nervous System				
Headache¶	20	0.7	23	0.7

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash maculo-papular, rash pruritic, rash pustular, rash macular, rash papular, butterfly rash, rash erythematous, eyelid rash
§ Includes cough, productive cough, upper-airway cough syndrome
¶ Includes headache, migraine, tension headache

Table 60: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving Intravenous Pembrolizumab with Chemotherapy in KEYNOTE-355

Laboratory Test*	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy		Placebo every 3 weeks with chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	90	20	85	19
Leukopenia	85	39	86	39
Neutropenia	78	50	79	53
Lymphopenia	73	28	71	19
Thrombocytopenia	54	19	53	21
Chemistry				
Increased ALT	60	11	58	8
Increased AST	57	9	55	6
Hyperglycemia	52	4.4	51	2.2
Hypoalbuminemia	36	2.0	32	2.2
Increased alkaline phosphatase	35	3.9	39	2.2
Hypocalcemia	29	3.3	27	1.8
Hyponatremia	28	5	26	6
Hypophosphatemia	21	7	18	4.8
Hypokalemia	20	4.4	18	4.0

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous pembrolizumab + chemotherapy (range: 566 to 592 patients) and placebo + chemotherapy (range: 269 to 280 patients).
† Graded per NCI CTCAE v4.03

Ovarian Cancer

The safety of intravenous pembrolizumab in combination with paclitaxel with or without bevacizumab was evaluated in 463 patients with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose

tumors express PD-L1 (CPS ≥1) enrolled in KEYNOTE-B96 *[see Clinical Studies (14.21)].* Among patients who received intravenous pembrolizumab, the median duration of exposure was 7.4 months (range: 1 day to 35.9 months).

Serious adverse reactions occurred in 54% of patients receiving intravenous pembrolizumab and paclitaxel with or without bevacizumab. Serious adverse reactions in ≥2% of patients were pneumonia (4.3%), urinary tract infection (3.9%), adrenal insufficiency (3%), hyponatremia (3%), COVID-19 (2.6%), decreased neutrophil count (2.6%), pulmonary embolism (2.6%), abdominal pain (2.1%), anemia (2.1%), colitis (2.1%), diarrhea (2.1%), febrile neutropenia (2.1%), pyrexia (2.1%) and vomiting (2.1%).

Fatal adverse reactions occurred in 3.9% of patients receiving intravenous pembrolizumab and paclitaxel with or without bevacizumab, including assisted suicide (0.9%), death (0.4%), intestinal perforation (0.4%), sepsis (0.4%), COVID-19 (0.4%), cardio-respiratory arrest (0.4%), colitis (0.4%), and embolic stroke (0.4%).

Intravenous pembrolizumab was permanently discontinued for adverse reactions in 16% of patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) were colitis (1.3%) and increased alanine aminotransferase (1.3%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 44% of patients. The most common adverse reactions leading to interruption of intravenous pembrolizumab in ≥2% were urinary tract infection (3.9%), adrenal insufficiency (2.6%), pyrexia (2.6%), pneumonitis (2.6%), upper respiratory tract infection (2.6%), neutropenia (2.1%), diarrhea (2.1%) and COVID-19 (2.1%).

The most common (≥20%) adverse reactions for patients treated with intravenous pembrolizumab in combination with paclitaxel with or without bevacizumab were: diarrhea (45%), fatigue (43%), nausea (41%), alopecia (38%), peripheral neuropathy (38%), epistaxis (31%), urinary tract infection (27%), constipation (25%), abdominal pain (24%), decreased appetite (24%), vomiting (24%), hypothyroidism (21%), cough (20%), hypertension (20%), and rash (20%). The most common (≥20%) laboratory abnormalities worsening from baseline were: anemia (85%), leukopenia (82%), decreased neutrophil count (71%), lymphopenia (60%), hypoalbuminemia (50%), hyponatremia (53%), hypomagnesemia (45%), increased aspartate aminotransferase (43%), increased alanine aminotransferase (40%), hypocalcemia(40%), increased alkaline phosphatase (31%), increased creatinine (29%), hypokalemia (27%) and neutropenia (21%).

For patients treated with intravenous pembrolizumab in combination with paclitaxel and bevacizumab (N=169), decreased white blood cell count (27%), stomatitis (22%) and pyrexia (21%) were also reported as adverse reactions.

6.2 Postmarketing Experience

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

Gastrointestinal: Exocrine pancreatic insufficiency

Hepatobiliary: sclerosing cholangitis

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, KEYTRUDA QLEX can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *(see Data)*. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

KEYTRUDA QLEX for subcutaneous injection contains pembrolizumab and berahyaluronidase alfa *[see Description (11)]*.

Pembrolizumab:

Animal reproduction studies have not been conducted with pembrolizumab to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects of the PD-1 pathway on reproduction demonstrated that a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering pembrolizumab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

Berahyaluronidase alfa:

In an embryo-fetal development study, pregnant rabbits were administered daily subcutaneous injections of 138,600, 403,200, or 1,209,600 U/kg berahyaluronidase alfa during the period of organogenesis (gestation days 6 to 19). Berahyaluronidase alfa caused delayed fetal development at doses ≥403,200 U/kg, which is >2,500 times higher than the human dose (U/kg basis). Increased post-implantation loss and visceral malformations (supernumerary fissure lung lobe) were observed at 1,209,600 U/kg, which is >7,500 times higher than the human dose. In an embryo-fetal development study in rats, there were no adverse embryo-fetal findings in pregnant animals administered daily subcutaneous injections of berahyaluronidase alfa at doses up to 2,520,000 U/kg (>15,000 times higher than the human dose) during the period of organogenesis (gestation days 6 to 17).

In a pre- and post-natal development study in rats, pregnant animals were administered daily subcutaneous injections of 280,000, 840,000, or 2,520,000 U/kg berahyaluronidase alfa from implantation through lactation and weaning (gestation day 6 to lactation day 21). There were no adverse effects on sexual maturation, learning and memory, or fertility of the offspring at doses up to 2,520,000 U/kg, which is >15,000 times higher than the human dose.

8.2 Lactation

Risk Summary

There are no data on the presence of pembrolizumab or berahyaluronidase alfa in either animal or human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk.

The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to KEYTRUDA QLEX are unknown. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KEYTRUDA QLEX and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, KEYTRUDA QLEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

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

Contraception

Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA QLEX and for 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of KEYTRUDA QLEX for the treatment of pediatric patients 12 years and older who weigh greater than 40 kg have been established for:

- Stage IIB, IIC, or III melanoma following complete resection *[see Indications and Usage (1.1)]*
- Unresectable or metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) solid tumors *[see Indications and Usage (1.6)]*
- Recurrent locally advanced or metastatic Merkel cell carcinoma *[see Indications and Usage (1.13)]*
- Unresectable or metastatic tumor mutational burden high solid tumors (TMB-H) *[see Indications and Usage (1.16)]*

Use of KEYTRUDA QLEX in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies of intravenous pembrolizumab in adults and additional pharmacokinetic and safety data for intravenous pembrolizumab in pediatric patients 12 years and older *[see Adverse Reactions (6.1), Clinical Studies (14)].* Pembrolizumab exposures in pediatric patients 12 years and older who weigh greater than 40 kg are predicted to be within range of those observed in adults at the same dosage *[see Clinical Pharmacology (12.3)].*

The safety and effectiveness of KEYTRUDA QLEX have not been established in pediatric patients younger than 12 years of age for the treatment of melanoma, MCC, MSI-H or dMMR cancer, and TMB-H cancer.

The safety and effectiveness of KEYTRUDA QLEX have not been established in pediatric patients for other approved indications *[see Indications and Usage (1)]*.

Intravenous pembrolizumab

In KEYNOTE-051, 173 pediatric patients (including 108 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H solid tumors received intravenous pembrolizumab 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 25 months). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults included pyrexia (33%), vomiting (29%), headache (25%), abdominal pain (23%), decreased lymphocyte count (13%), and decreased white blood cell count (11%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (30%), neutropenia (28%), thrombocytopenia (22%), and Grade 3 anemia (17%).

8.5 Geriatric Use

Of the 251 patients treated with KEYTRUDA QLEX in combination with platinum doublet chemotherapy in Study MK-3745A-D77, 53% were 65 years and older and 16% were 75 years and older. No overall differences in safety or effectiveness of KEYTRUDA QLEX have been observed between patients aged 65 years or older and younger adult patients.

The safety of KEYTRUDA QLEX as monotherapy or in combination with other antineoplastic drugs for its approved indications *[see Indications and Usage (1)]* has been established in adequate and well-controlled studies of intravenous pembrolizumab as a single agent and in combination with other antineoplastic drugs. Below is a description of geriatric use information from the intravenous pembrolizumab studies.

- Of 3781 patients with melanoma, NSCLC, HNSCC, or urothelial carcinoma who were treated with intravenous pembrolizumab in clinical studies, 48% were 65 years and over and 17% were 75 years and over.

- Of 506 adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC following complete resection and platinum-based chemotherapy who were treated with intravenous pembrolizumab in KEYNOTE-091, 242 (48%) were 65 years and over.
- Of 221 adult patients with TNBC who were treated with intravenous pembrolizumab in combination with sacituzumab govitecan-hziy in KEYNOTE-D19, 26% of patients were 65 years and over and 5% were 75 years and older. No overall differences in effectiveness were observed between elderly patients and younger patients. There was a higher rate of serious adverse reactions in patients aged 65 years or older (48%) compared with younger adult patients (34%).
- Of 596 adult patients with TNBC who were treated with intravenous pembrolizumab in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin in KEYNOTE-355, 137 (23%) were 65 years and over.
- Of 406 adult patients with endometrial carcinoma who were treated with intravenous pembrolizumab in combination with lenvatinib in KEYNOTE-775, 201 (50%) were 65 years and over.
- Of the 564 patients with locally advanced or metastatic urothelial cancer treated with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.
- Of the 570 patients with MIBC treated with intravenous pembrolizumab in combination with enfortumab vedotin-ejfy, 45% (n=259) were 65-74 years and 22% (n=125) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with intravenous pembrolizumab in combination with enfortumab vedotin-ejfv experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 3.6% in patients younger than 75 and 11% in patients 75 years or older.
- Of the 432 patients randomized to intravenous pembrolizumab in combination with axitinib in the KEYNOTE-426 trial, 40% were 65 years or older.
- Of 294 adult patients with FIGO 2014 Stage III-IVA cervical cancer who were treated with intravenous pembrolizumab in combination with CRT in KEYNOTE-A18, 42 (14%) were 65 years and over.
- Of 643 adult patients with ovarian cancer who were treated with intravenous pembrolizumab in combination with paclitaxel with or without bevacizumab in KEYNOTE-B96, 236 (37%) were 65 years and over and 58 (9%) were 75 years and over.

No overall differences in safety or effectiveness were observed between intravenous pembrolizumab-treated patients aged 65 years or older and younger adult patients.

11 DESCRIPTION

KEYTRUDA QLEX is a fixed-combination drug product containing pembrolizumab and berahyaluronidase alfa.

Pembrolizumab is a programmed death receptor-1 (PD 1)-blocking antibody. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

Berahyaluronidase alfa is an endoglycosidase used to enhance dispersion and permeation, which facilitates delivery of increased volume of pembrolizumab that is co-administered subcutaneously. It is produced by mammalian CHO (Chinese Hamster Ovary) cells containing a DNA plasmid encoding a variant of human hyaluronidase PH20. It is a glycosylated protein with an approximate molecular weight of 49 kDa under nonreducing, deglycosylated conditions.

KEYTRUDA QLEX (pembrolizumab and berahyaluronidase alfa-pmph) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution supplied in single-dose vials for subcutaneous administration.

KEYTRUDA QLEX is supplied as two different configurations:

- Each KEYTRUDA QLEX 2.4 mL single-dose vial contains 395 mg of pembrolizumab and 4,800 units of berahyaluronidase alfa, and histidine (0.7 mg), histidine hydrochloride monohydrate (4.1 mg), methionine (3.6 mg), polysorbate 80 (0.5 mg), sucrose (168 mg), and Water for Injection, USP. The pH is 5.3-5.9.
- Each KEYTRUDA QLEX 4.8 mL single-dose vial contains 790 mg of pembrolizumab and 9,600 units of berahyaluronidase alfa, and histidine (1.4 mg), histidine hydrochloride monohydrate (8.2 mg), methionine (7.2 mg), polysorbate 80 (1 mg), sucrose (336 mg), and Water for Injection, USP. The pH is 5.3-5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

In syngeneic mouse tumor models, combination treatment of a PD-1 blocking antibody and kinase inhibitor lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and reduced tumor growth compared to either treatment alone.

Berahyaluronidase alfa, an endoglycosidase, is a variant of human hyaluronidase PH20 that temporarily and locally breaks down hyaluronan. Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan.

In the doses administered, the effects of berahyaluronidase alfa are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

12.2 Pharmacodynamics

There are no clinically significant exposure-response relationships for efficacy or safety for intravenous pembrolizumab across the approved dosing regimens, regardless of cancer type. The exposures from subcutaneous KEYTRUDA QLEX doses of 395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks are within the range of exposures from intravenous pembrolizumab doses.

12.3 Pharmacokinetics

Pembrolizumab pharmacokinetics were characterized at Cycle 1 and at steady state in patients with advanced solid tumors at the approved recommended dosages and are presented as mean (CV%) unless otherwise specified.

When comparing pembrolizumab exposure following subcutaneous administration every 6 weeks to that of intravenous administration every 6 weeks in Study MK-3475A-D77 *[see Clinical Studies (14.1)],* the geometric mean ratio (GMR) for Cycle 1 $AUC_{0\text{-}6wks}$ was 1.14 (96% CI: 1.06, 1.22) and Cycle 3 C_{trough} (i.e., steady state) was 1.67 (94% CI: 1.52, 1.84).

Pembrolizumab steady state was reached by 16 weeks. At steady state following subcutaneous administration, the mean pembrolizumab $AUC_{0\text{-}6wks}$ was 2,798 mcg•day/mL for the every 6 week dosing and pembrolizumab $AUC_{0\text{-}3wks}$ was 1,343 mcg•day/mL for the every 3 week dosing. Pembrolizumab C_{trough} was 39 mcg/mL for the every 6 week dosing and 49 mcg/mL for the every 3 week dosing.

The systemic accumulation ratio was 1.6-fold following administration of KEYTRUDA QLEX 790 mg/9,600 units every 6 weeks and 2.5-fold following administration of KEYTRUDA QLEX 395 mg/4,800 units every 3 weeks.

Absorption

Pembrolizumab bioavailability (CV%) is approximately 60% (14%). Peak concentrations occurred by approximately 4 days.

Distribution

The volume of distribution is 6 L.

Elimination

Pembrolizumab clearance decreases over time, resulting in a steady state clearance (CV%) of 195 mL/day (40%); this decrease in clearance with time is not considered clinically significant. The terminal half-life is 22 days.

Specific Populations

No clinically significant differences in the pharmacokinetics of pembrolizumab were observed based on age (37 to 87 years), race (63% White, 28% Asian, 3% Black), sex, body weight (37 to 144 kg), tumor type, injection site (thigh or abdomen), estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2, and mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST). The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST) on pembrolizumab pharmacokinetics is unknown.

Pediatric Patients

Pembrolizumab exposures in pediatric patients 12 years and older who weigh greater than 40 kg are predicted to be within range of those observed in adult patients at the same dosage.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described in this section with the incidence of ADA in other studies, including those of KEYTRUDA QLEX or of other pembrolizumab products or berahyaluronidase alfa products.

With a median (min, max) duration of treatment on KEYTRUDA QLEX of 6.9 months (1 day, 1 year) in Study MK-3475A-D77, 1.4% (3/211) of patients developed anti-pembrolizumab antibodies, and one ADA-positive patient developed neutralizing antibodies (NAb) against pembrolizumab. The incidence of anti-berahyaluronidase alfa antibodies was 1.5% (3/194). No analysis of neutralizing antibodies was performed for berahyaluronidase alfa ADA-positive samples. Because of the low occurrence of anti-pembrolizumab or anti-berahyaluronidase antibodies, the effect of these antibodies on the pharmacokinetics, safety and effectiveness of KEYTRUDA QLEX is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

KEYTRUDA QLEX contains pembrolizumab and berahyaluronidase alfa.

Pembrolizumab

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

Berahyaluronidase alfa

Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of berahyaluronidase alfa.

In a fertility and early embryonic development study, male and female rats were administered daily subcutaneous injections of 280,000, 840,000, or 2,520,000 U/kg berahyaluronidase alfa. Males were dosed for 9 weeks prior to mating and throughout mating to termination. Females were dosed for 2 weeks prior to mating, throughout mating, and up to gestation day 7. Although treatment with ≥840,000 U/kg berahyaluronidase alfa (>5,200 times higher than the human dose) resulted in an increased incidence of abnormal sperm morphology, there were no adverse effects on mating, fertility or embryogenesis observed at doses up to 2,520,000 U/kg (>15,000 times higher than the human dose).

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1/PD-L1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice and mice receiving PD-L1-blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus. Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 KEYTRUDA QLEX

NSCLC (Study MK-3475A-D77)

KEYTRUDA QLEX was evaluated in Study MK-3475A-D77 (NCT05722015), a randomized, multicenter, open-label, active-controlled trial conducted in patients with treatment-naïve metastatic NSCLC, in whom there were no EGFR, ALK, or ROS1 genomic tumor aberrations. Patients were excluded if they had a history of autoimmune disease that required systemic therapy within 2 years of treatment; had a medical condition that required immunosuppression; or had received more than 30 Gy of thoracic radiation within the prior 26 weeks.

A total of 377 patients were randomized (2:1) to receive either KEYTRUDA QLEX (containing 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa) administered subcutaneously every 6 weeks with platinum doublet chemotherapy (n=251) or pembrolizumab 400 mg intravenously every 6 weeks with platinum doublet chemotherapy (n=126).

The chemotherapy regimens were as follows:

- Non-squamous NSCLC: pemetrexed 500 mg/m^2 and a platinum chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min) intravenously every 3 weeks for 4 cycles, followed by pemetrexed 500 mg/m^2 intravenously every 3 weeks.
- Squamous NSCLC: carboplatin AUC 6 mg/mL/min and a taxane (paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle) intravenously every 3 weeks for 4 cycles.

Randomization was stratified by ECOG performance status (0 vs. 1), histology (squamous vs. non-squamous), PD-L1 TPS (<50% vs. ≥50%), and geographic region (East Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World).

Treatment with KEYTRUDA QLEX or intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 18 cycles (approximately 24 months). Administration of KEYTRUDA QLEX or intravenous pembrolizumab

was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

The primary outcome measure was pembrolizumab exposure [Cycle 1 $AUC_{0\text{-}6\ weeks}$ and Cycle 3 (i.e., Steady State) C_{trough}] of subcutaneous KEYTRUDA QLEX as compared to intravenous pembrolizumab *[see Clinical Pharmacology (12.3)]*. Additional descriptive efficacy outcome measures were overall response rate (ORR) by blinded independent central review (BICR), progression-free survival (PFS) by BICR, and overall survival (OS).

The study population characteristics were: median age 65 years (range: 37 to 87); 71% male; 63% White, 29% Asian, 4% multiracial, 3% Black or African American, 2% American Indian or Alaska Native; 31% of Hispanic or Latino ethnicity; 35% ECOG performance status (PS) of 0 and 65% ECOG PS of 1. Nineteen percent had PD-L1 TPS ≥50%; 34% had tumors with squamous histology and 66% had tumors with non-squamous histology; and 9% had brain metastases at baseline.

At the primary analysis, the confirmed ORR was 45% (95% CI: 39, 52) in the subcutaneous KEYTRUDA QLEX arm and 42% (95% CI: 33, 51) in the intravenous pembrolizumab arm. There were no notable differences in PFS or OS observed in patients who received KEYTRUDA QLEX compared to patients who received intravenous pembrolizumab.

Intravenous Pembrolizumab

The effectiveness of KEYTRUDA QLEX for its approved indications *[see Indications and Usage (1)]* has been established based upon the evidence from the adequate and well-controlled studies conducted with intravenous pembrolizumab *[see Clinical Studies (14.3-14.21)]* and additional data that demonstrated comparable pharmacokinetic, efficacy, and safety profiles between KEYTRUDA QLEX and intravenous pembrolizumab in Study MK-3475A-D77 *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].*

Below is a description of the efficacy results of these adequate and well-controlled studies of intravenous pembrolizumab in these patient populations.

14.2 Patient Experience

Study MK-3475A-F11 (NCT06099782) was a randomized, multicenter, open-label, cross-over trial conducted in 147 patients with early-stage or advanced/metastatic solid tumors [resected stage IIB, IIC, or III melanoma (n=56); or intermediate-high or high-risk resected RCC (n=45); or newly diagnosed, untreated Stage IV NSCLC with a PD-L1 TPS ≥50% (n=46)]. Patients were randomized (1:1) to receive 3 cycles of KEYTRUDA QLEX 395 mg/4,800 units subcutaneously every 3 weeks followed by 3 cycles of pembrolizumab 200 mg intravenously every 3 weeks (Arm A – SC/IV; n=71) or 3 cycles of pembrolizumab 200 mg intravenously every 3 weeks followed by 3 cycles of KEYTRUDA QLEX 395 mg/4,800 units subcutaneously every 3 weeks (Arm B – IV/SC; n=76).

On Day 1 of Cycle 6, 118 out of 122 eligible patients (97%) completed the patient preference questionnaire (PPQ) after receiving treatment. Seventy-seven of the 118 patients (65%) reported preferring subcutaneous administration of KEYTRUDA QLEX over intravenous pembrolizumab and the most common reason was that it required less time in the clinic. Thirty-eight of the 118 patients (32%) reported preferring intravenous pembrolizumab over KEYTRUDA QLEX and the most common reason was that it felt more comfortable during administration. Three of the 118 patients (3%) had no preference for the route of administration.

Patients in both arms could continue to receive treatment after the crossover period for up to 17 cycles (resected RCC and melanoma) or 35 cycles (stage IV NSCLC). Of the 122 patients who completed Cycle 6, 83 (68%) patients (35 from SC/IV and 48 from IV/SC) chose to continue treatment with the subcutaneous route of administration over the intravenous route of administration.

14.3 Melanoma

Ipilimumab-Naive Melanoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-006 (NCT01866319), a randomized (1:1:1), open-label, multicenter, active-controlled trial in 834 patients. Patients were randomized to receive intravenous pembrolizumab at a dose of 10 mg/kg intravenously every 2 weeks or 10 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review [BICR] using Response Evaluation Criteria in Solid Tumors [RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ]). Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DoR).

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 66% had no prior systemic therapy for metastatic disease; 69% ECOG PS of 0; 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay; 65% had M1c stage disease; 68% with normal LDH; 36% with reported BRAF mutation-positive melanoma; and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

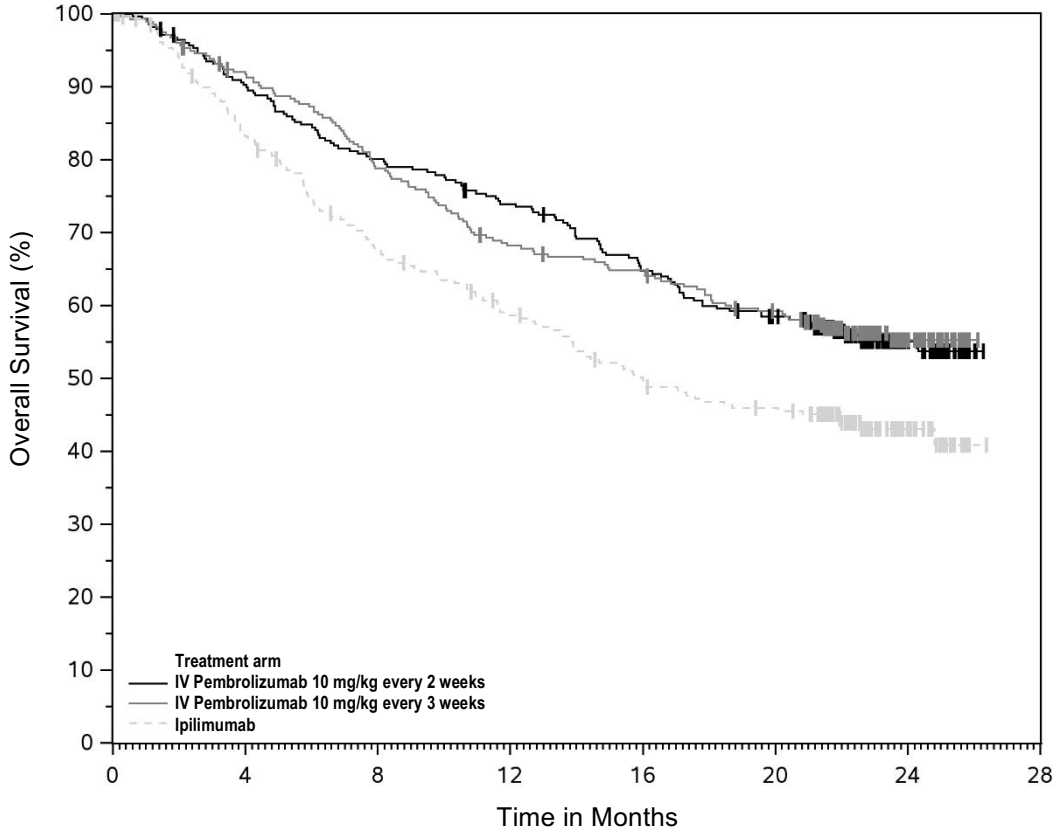
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to intravenous pembrolizumab as compared to ipilimumab. Among the 91 patients randomized to intravenous pembrolizumab 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to intravenous pembrolizumab 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months. Efficacy results are summarized in Table 61 and Figure 1.

Table 61: Efficacy Results in KEYNOTE-006

Endpoint	Intravenous Pembrolizumab 10 mg/kg every 3 weeks n=277	Intravenous Pembrolizumab 10 mg/kg every 2 weeks n=279	Ipilimumab 3 mg/kg every 3 weeks n=278
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best objective response by BICR			
ORR (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response rate	6%	5%	1%
Partial response rate	27%	29%	10%

* Hazard ratio (intravenous pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

Figure 1: Kaplan-Meier Curve for Overall Survival in KEYNOTE-006*



Number at Risk								
IV Pembrolizumab 10 mg/kg every 2 weeks	279	249	221	202	176	156	44	0
IV Pembrolizumab 10 mg/kg every 3 weeks	277	251	215	184	174	156	43	0
Ipilimumab	278	213	170	145	122	110	28	0

*Based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)

Ipilimumab-Refractory Melanoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-002 (NCT01704287), a multicenter, randomized (1:1:1), active-controlled trial in 540 patients randomized to receive one of two doses of intravenous pembrolizumab in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of intravenous pembrolizumab 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 mg/mL/min intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 mg/mL/min plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 mg/mL/min intravenously every 3 weeks (8%). Randomization was stratified by ECOG PS (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received intravenous pembrolizumab until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was

confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered intravenous pembrolizumab. The major efficacy outcomes were PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. Additional efficacy outcome measures were confirmed ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age of 62 years (range: 15 to 89), 43% age 65 or older; 61% male; 98% White; and 55% ECOG PS of 0 and 45% ECOG PS of 1. Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to intravenous pembrolizumab as compared to control arm. There was no statistically significant difference between intravenous pembrolizumab 2 mg/kg and chemotherapy or between intravenous pembrolizumab 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive intravenous pembrolizumab. Among the 38 patients randomized to intravenous pembrolizumab 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to intravenous pembrolizumab 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months. Efficacy results are summarized in Table 62 and Figure 2.

Table 62: Efficacy Results in KEYNOTE-002

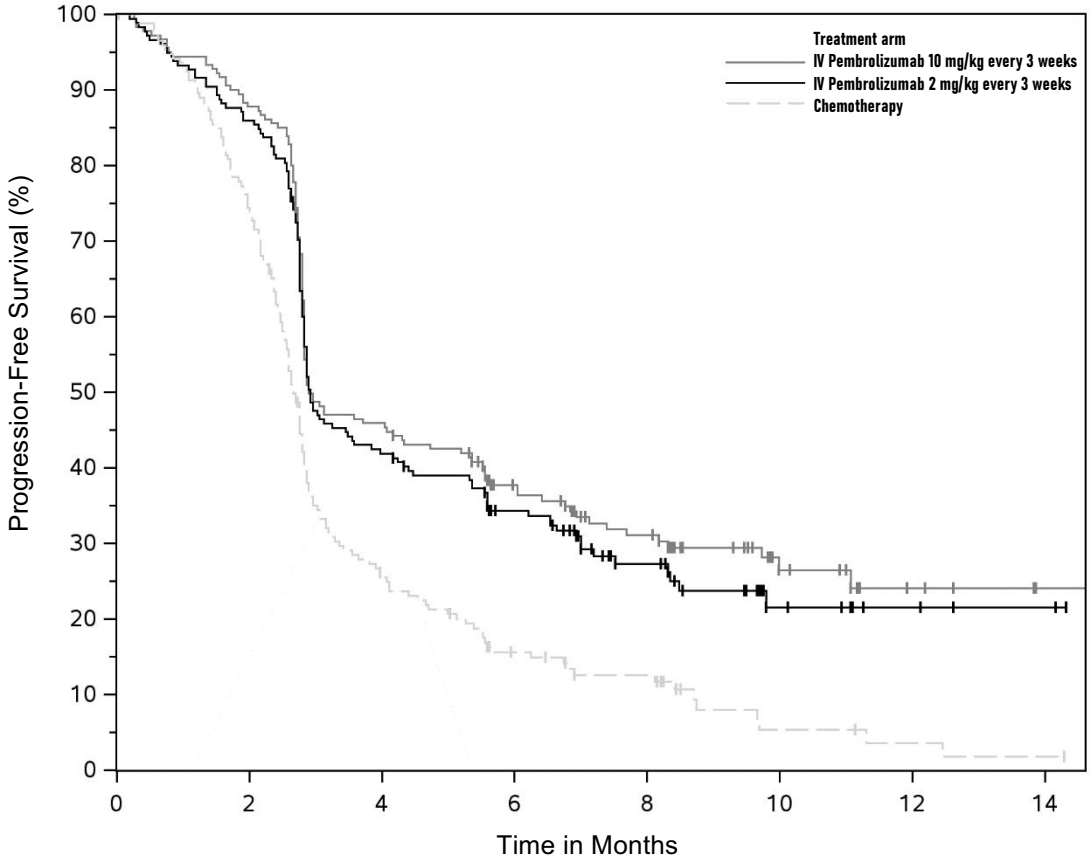
Endpoint	**Intravenous Pembrolizumab 2 mg/kg every 3 weeks n=180**	**Intravenous Pembrolizumab 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
p-Value (stratified log-rank)	<0.001	<0.001	---
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
OS†			
Deaths (%)	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value (stratified log-rank)	0.117	0.011‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Objective Response Rate			
ORR (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response rate	2%	3%	0%
Partial response rate	19%	23%	4%

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

† With additional follow-up of 18 months after the PFS analysis

‡ Not statistically significant compared to multiplicity adjusted significance level of 0.01

Figure 2: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-002



Number at Risk								
IV Pembrolizumab 10 mg/kg	181	158	82	55	39	15	5	1
IV Pembrolizumab 2 mg/kg	180	153	74	53	26	9	4	2
Chemotherapy	179	128	43	22	15	4	2	1

Adjuvant Treatment of Resected Stage IIB or IIC Melanoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-716 (NCT03553836), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected Stage IIB or IIC melanoma. Patients were randomized to intravenous pembrolizumab 200 mg or the pediatric (≥12 years old) dose of intravenous pembrolizumab 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by AJCC 8th edition T Stage (>2.0-4.0 mm with ulceration vs. >4.0 mm without ulceration vs. >4.0 mm with ulceration). Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) (defined as the time between the date of randomization and the date of first recurrence [local, in-transit or regional lymph nodes or distant recurrence] or death, whichever occurred first). New primary melanomas were excluded from the definition of RFS. Distant metastasis-free survival (DMFS), defined as a spread of tumor to distant organs or distant lymph nodes, was an additional efficacy outcome measure. Patients underwent imaging every six months for one year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

The study population characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; 98% White; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had Stage IIB and 35% had Stage IIC.

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the intravenous pembrolizumab arm compared with placebo. Efficacy results are summarized in Table 63 and Figure 3.

Table 63: Efficacy Results in KEYNOTE-716

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=487	Placebo n=489
RFS		
Number (%) of patients with event	54 (11%)	82 (17%)
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio*,† (95% CI)	0.65 (0.46, 0.92)	
p-Value†	0.0132‡	
DMFS		
Number (%) of patients with event	63 (13%)	95 (19%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio*,† (95% CI)	0.64 (0.47, 0.88)	
p-Value†	0.0058§	

* Based on the stratified Cox proportional hazard model

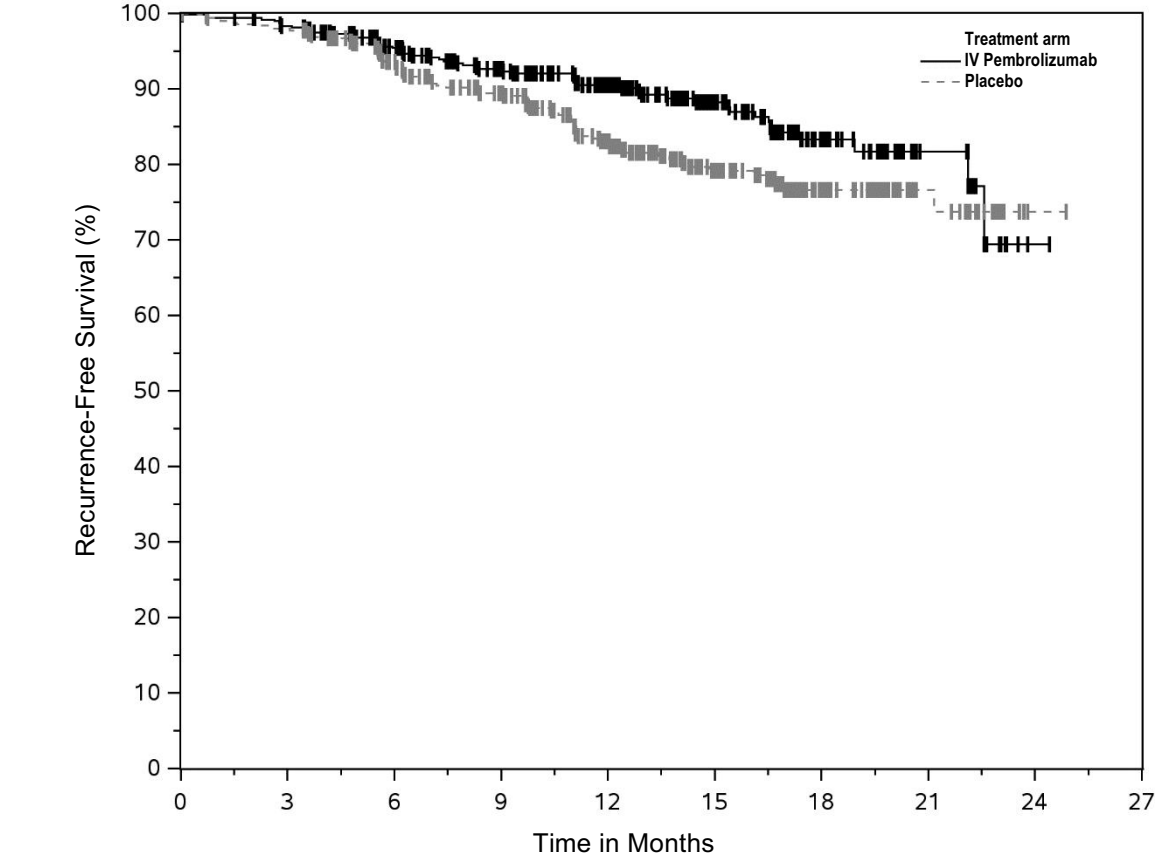
† Based on a log-rank test stratified by American Joint Committee on Cancer 8th edition (AJCC) stage

‡ p-Value is compared with 0.0202 of the allocated alpha for this interim analysis.

§ p-Value is compared with 0.0256 of the allocated alpha for this interim analysis.

NR = not reached

Figure 3: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716



Number at Risk										
IV Pembrolizumab	487	465	401	340	249	149	71	21	1	0
Placebo	489	475	400	336	229	149	77	27	1	0

Adjuvant Treatment of Stage III Resected Melanoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-054 (NCT02362594), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected Stage IIIA (>1 mm lymph node metastasis), IIIB, or IIIC melanoma. Patients were randomized to intravenous pembrolizumab 200 mg intravenously every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. New primary melanomas were excluded from the definition of RFS. DMFS in the whole population and in the population with PD-L1 positive tumors were additional efficacy outcome measures. DMFS was defined as

a spread of tumor to distant organs or distant lymph nodes. Patients underwent imaging every 12 weeks after the first dose of intravenous pembrolizumab for the first two years, then every 6 months from year 3 to 5, and then annually.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had Stage IIIA, 46% had Stage IIIB, 18% had Stage IIIC (1-3 positive lymph nodes), and 20% had Stage IIIC (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IUO assay.

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the intravenous pembrolizumab arm compared with placebo. Efficacy results are summarized in Table 64 and Figure 4.

Table 64: Efficacy Results in KEYNOTE-054

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=514	Placebo n=505
RFS		
Number (%) of patients with event	135 (26%)	216 (43%)
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio*,† (95% CI)	0.57 (0.46, 0.70)	
p-Value† (log-rank)	<0.001±	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
Median in months (95% CI)	NR (49.6, NR)	40.0 (27.7, NR)
Hazard ratio*,† (95% CI)	0.60 (0.49, 0.73)	
p-Value† (log-rank)	<0.0001§	

* Based on the stratified Cox proportional hazard model

† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage

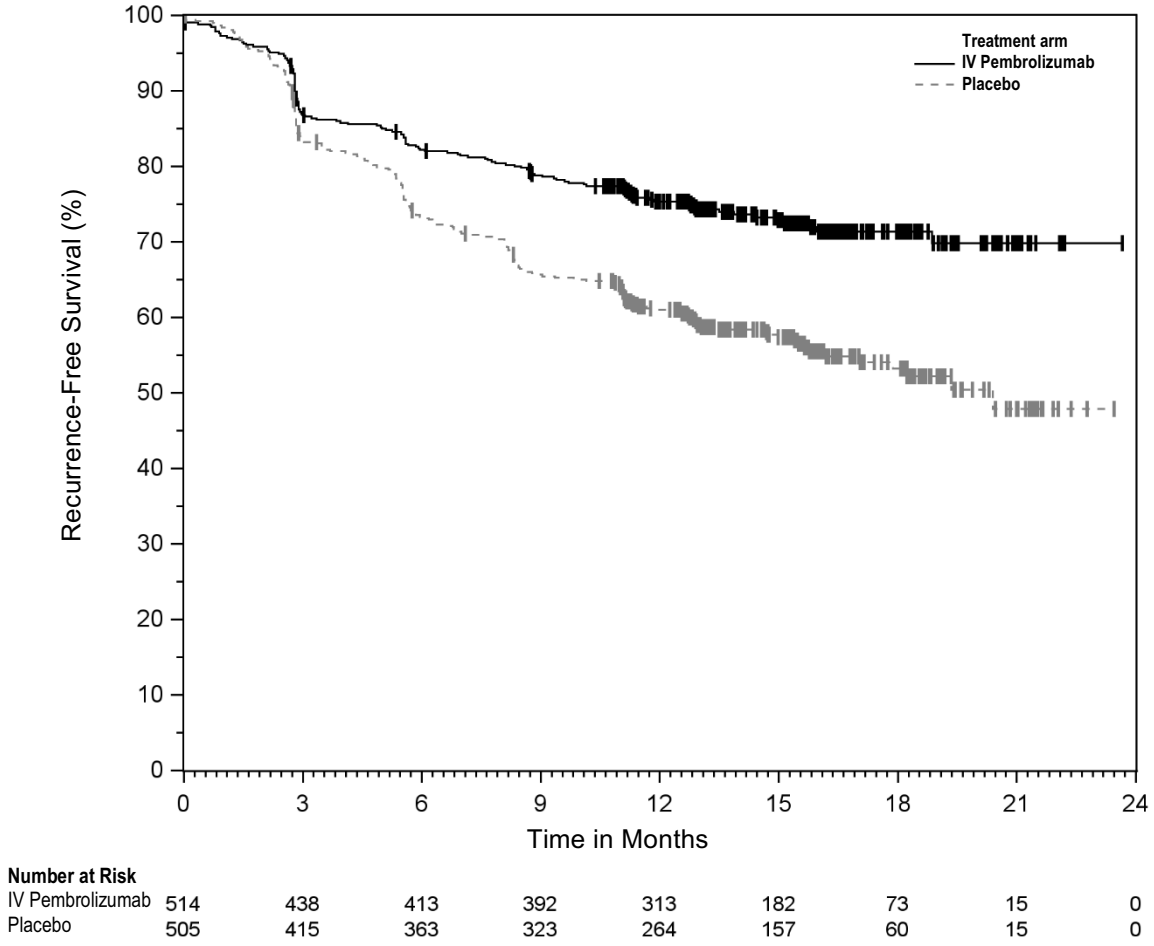
± p-Value is compared with 0.016 of the allocated alpha for this interim analysis.

§ p-Value is compared with 0.028 of the allocated alpha for this analysis.

NR = not reached

For patients with PD-L1 positive tumors, the RFS HR was 0.54 (95% CI: 0.42, 0.69); p<0.0001. For patients with PD-L1 positive tumors, the DMFS HR was 0.61 (95% CI: 0.49, 0.76); p<0.0001. The RFS and DMFS benefit for intravenous pembrolizumab compared to placebo was observed regardless of tumor PD-L1 expression.

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054



14.4 Non-Small Cell Lung Cancer

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The efficacy of intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms:

- Intravenous pembrolizumab 200 mg, pemetrexed 500 mg/m^2, and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by intravenous pembrolizumab 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks.

- Placebo, pemetrexed 500 mg/m^2, and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 intravenously every 3 weeks.

Treatment with intravenous pembrolizumab continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of intravenous pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Patients randomized to placebo and chemotherapy were offered intravenous pembrolizumab as a single agent at the time of disease progression. Assessment of tumor status was performed at Week 6, Week 12, and then every 9 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG PS of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% [negative]. Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/PD-L1 monoclonal antibody at the time of disease progression.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 65 and Figure 5 summarize the efficacy results for KEYNOTE-189.

Table 65: Efficacy Results in KEYNOTE-189

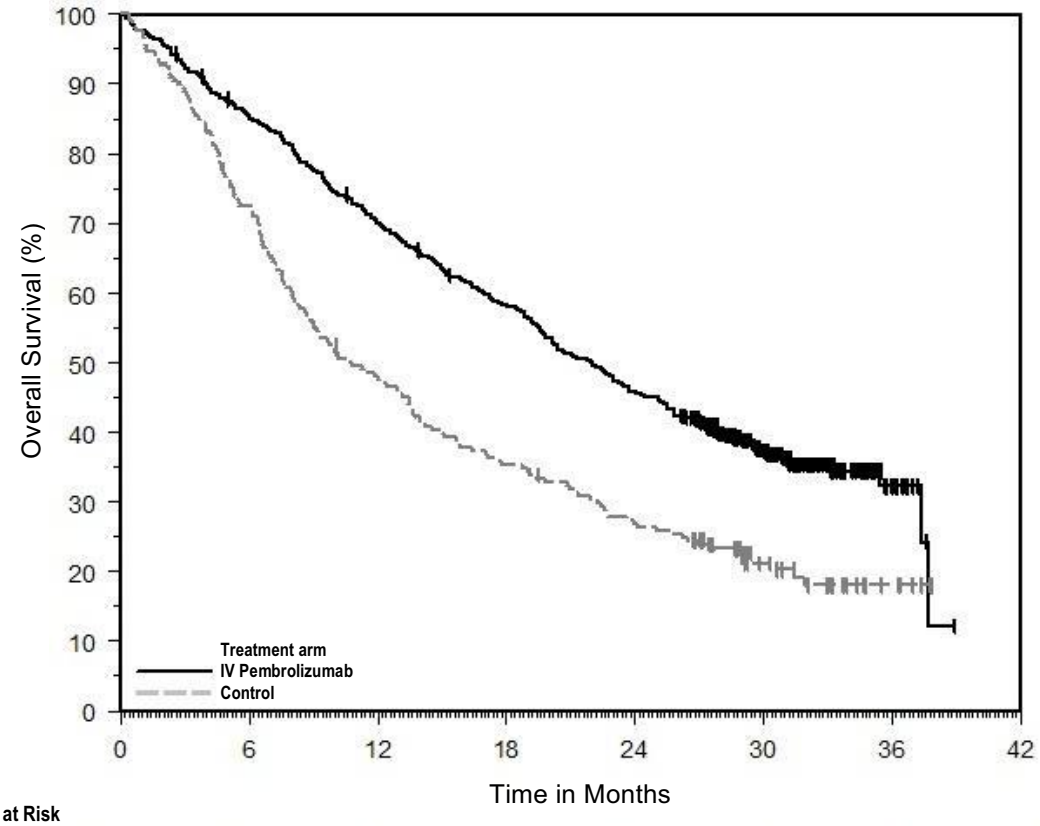
Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=410	Placebo Pemetrexed Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Median in months (95% CI)	NR (NR, NR)	11.3 (8.7, 15.1)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.0001	
PFS		
Number of patients with event (%)	245 (60%)	166 (81%)
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy, and smoking status
NR = not reached

At the protocol-specified final OS analysis, the median in the intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy arm was 22.0 months (95% CI: 19.5, 24.5) compared to

10.6 months (95% CI: 8.7, 13.6) in the placebo with pemetrexed and platinum chemotherapy arm, with an HR of 0.56 (95% CI: 0.46, 0.69).

Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-189*



Number at Risk								
IV Pembrolizumab	410	347	283	234	184	86	12	0
Control	206	149	98	72	55	25	5	0

*Based on the protocol-specified final OS analysis

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy

The efficacy of intravenous pembrolizumab in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%), choice of paclitaxel or paclitaxel protein-bound, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- Intravenous pembrolizumab 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by intravenous pembrolizumab 200 mg every 3 weeks.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with intravenous pembrolizumab and chemotherapy or placebo and chemotherapy continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of intravenous pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients randomized to the placebo and chemotherapy arm were offered intravenous pembrolizumab as a single agent at the time of disease progression. Assessment of tumor status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The main efficacy outcome measures were PFS and ORR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. An additional efficacy outcome measure was DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 29 to 88), 55% age 65 or older; 81% male; 77% White; 71% ECOG PS of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS <1%; 19% were from the East Asian region; and 60% received paclitaxel.

The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to intravenous pembrolizumab in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 66 and Figure 6 summarize the efficacy results for KEYNOTE-407.

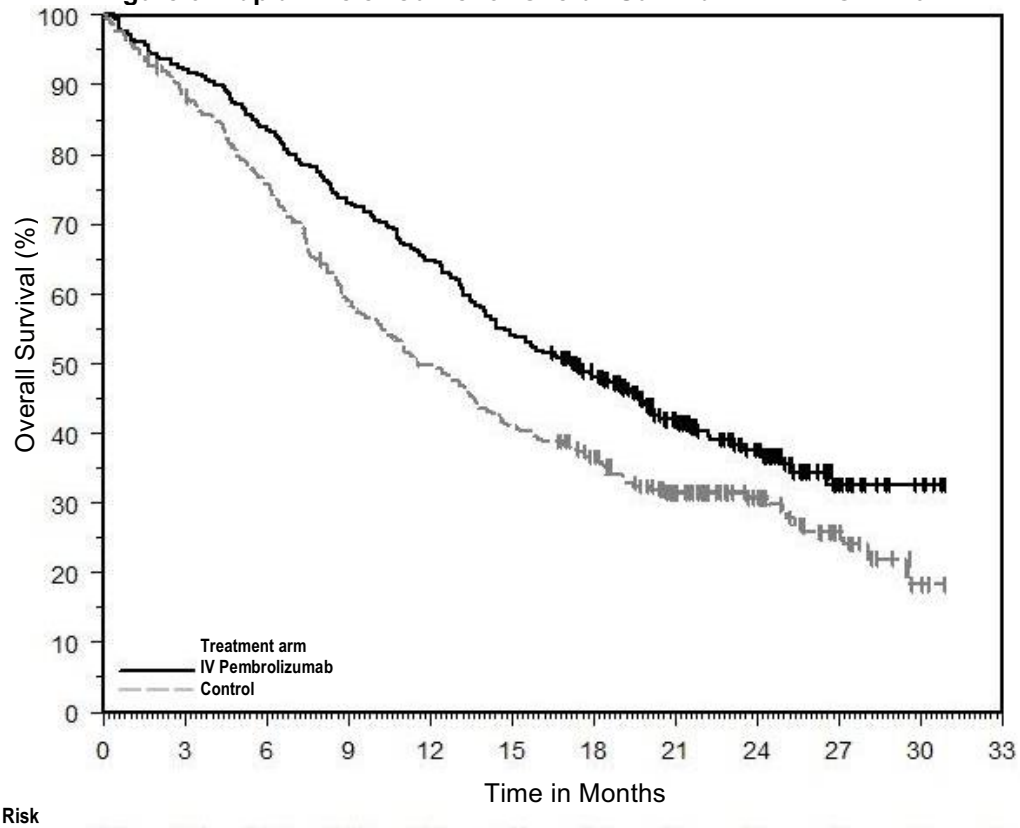
Table 66: Efficacy Results in KEYNOTE-407

Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks Carboplatin Paclitaxel/Paclitaxel protein-bound n=278**	**Placebo Carboplatin Paclitaxel/Paclitaxel protein-bound n=281**
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NE)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value†	0.0017	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.2, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value†	<0.0001	
	n=101	**n=103**
Objective Response Rate‡		
ORR (95% CI)	58% (48, 68)	35% (26, 45)
Difference (95% CI)	23.6% (9.9, 36.4)	
p-Value§	0.0008	
Duration of Response‡		
Median duration of response in months (range)	7.2 (2.4, 12.4+)	4.9 (2.0, 12.4+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ ORR primary analysis and DoR analysis were conducted with the first 204 patients enrolled.
§ Based on a stratified Miettinen-Nurminen test
NE = not estimable

At the protocol-specified final OS analysis, the median in the intravenous pembrolizumab in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm was 17.1 months (95% CI: 14.4, 19.9) compared to 11.6 months (95% CI: 10.1, 13.7) in the placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm, with an HR of 0.71 (95% CI: 0.58, 0.88).

Figure 6: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407*



Number at Risk												
IV Pembrolizumab	278	256	232	203	180	150	119	80	46	14	4	0
Control	281	245	210	163	137	113	91	61	36	16	3	0

*Based on the protocol-specified final OS analysis

First-line treatment of metastatic NSCLC with PD-L1 expression (TPS ≥1%) as a single agent

KEYNOTE-042

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with Stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx assay and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥50% vs. TPS 1 to 49%). Patients were randomized (1:1) to receive intravenous pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of either of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies.

Treatment with intravenous pembrolizumab continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of intravenous pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Treatment with intravenous pembrolizumab could be reinitiated at the time of subsequent disease progression and administered for up to 12 months. Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measure was OS in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC. Additional efficacy outcome measures were PFS and ORR in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Sixty-nine percent had ECOG PS of 1; 39% with squamous and 61% with nonsquamous histology; 87% had M1 disease and 13% had Stage IIIA (2%) or Stage IIIB (11%) and who were not candidates for surgical resection or definitive chemoradiation per investigator assessment; and 5% with treated brain metastases at baseline. Forty-seven percent of patients had TPS ≥50% NSCLC and 53% had TPS 1 to 49% NSCLC.

The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to intravenous pembrolizumab as compared with chemotherapy. Table 67 and Figure 7 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

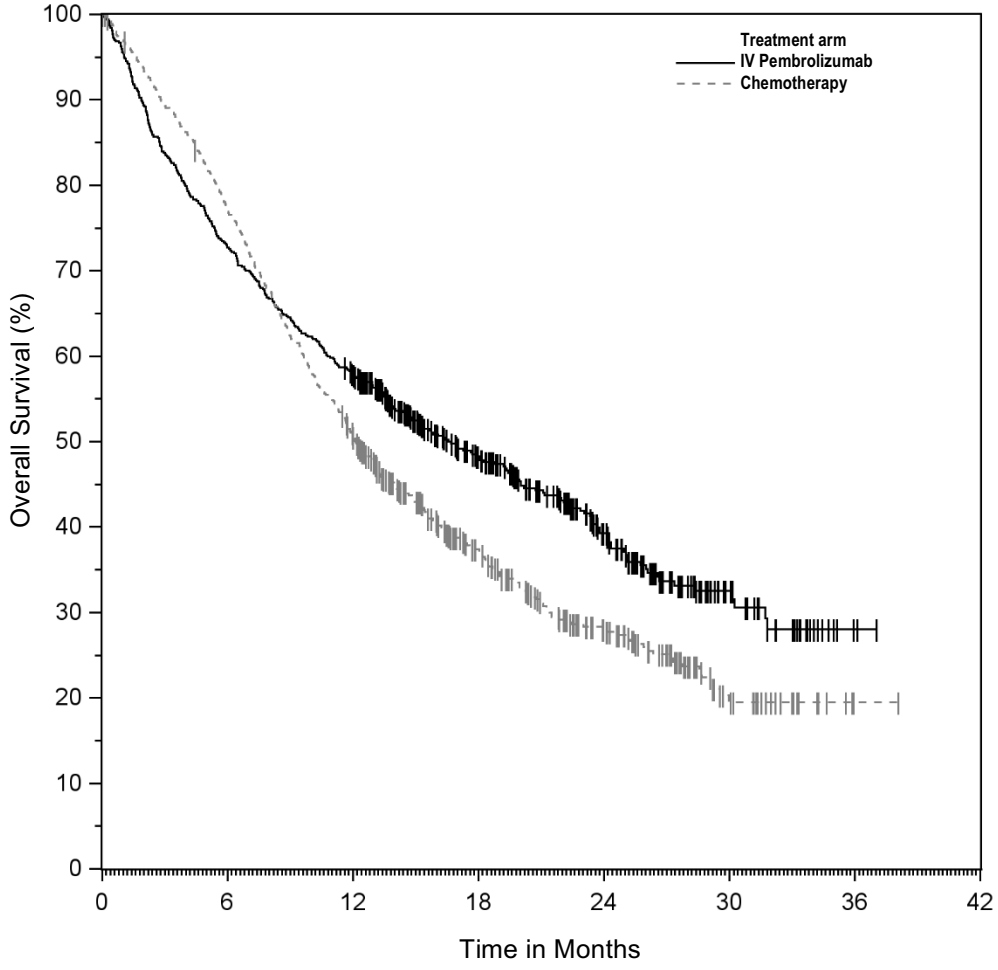
Table 67: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	TPS ≥1%		**TPS ≥50%**	
Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks n=637**	**Chemotherapy n=637**	**Intravenous Pembrolizumab 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS				
Number of events (%)	371 (58%)	438 (69%)	157 (53%)	199 (66%)
Median in months (95% CI)	16.7 (13.9, 19.7)	12.1 (11.3, 13.3)	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)
Hazard ratio* (95% CI)	0.81 (0.71, 0.93)		0.69 (0.56, 0.85)	
p-Value†	0.0036		0.0006	
PFS				
Number of events (%)	507 (80%)	506 (79%)	221 (74%)	233 (78%)
Median in months (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)	6.9 (5.9, 9.0)	6.4 (6.1, 6.9)
Hazard ratio*,‡ (95% CI)	1.07 (0.94, 1.21)		0.82 (0.68, 0.99)	
p-Value†	-‡		NS§	
Objective Response Rate				
ORR‡ (95% CI)	27% (24, 31)	27% (23, 30)	39% (33.9, 45.3)	32% (26.8, 37.6)
Complete response rate	0.5%	0.5%	0.7%	0.3%
Partial response rate	27%	26%	39%	32%
Duration of Response				
% with duration ≥12 months¶	47%	16%	42%	17%
% with duration ≥18 months¶	26%	6%	25%	5%

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test; compared to a p-Value boundary of 0.0291
‡ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints
§ Not significant compared to a p-Value boundary of 0.0291
¶ Based on observed duration of response

The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≥50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11).

Figure 7: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-042 (TPS ≥1%)



Number at Risk								
IV Pembrolizumab	637	463	365	214	112	35	2	0
Chemotherapy	637	485	316	166	88	24	1	0

KEYNOTE-024

The efficacy of intravenous pembrolizumab was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx assay were eligible. Patients were randomized (1:1) to receive intravenous pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of any of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for nonsquamous histologies).

Patients randomized to chemotherapy were offered intravenous pembrolizumab at the time of disease progression.

The main efficacy outcome measure was PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were OS and ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 33 to 90), 54% age 65 or older; 61% male; 82% White and 15% Asian; 65% with ECOG PS of 1; 18% with squamous and 82% with nonsquamous histology and 9% with history of brain metastases. A total of 66 patients in the chemotherapy arm received intravenous pembrolizumab at the time of disease progression.

The trial demonstrated a statistically significant improvement in both PFS and OS for patients randomized to intravenous pembrolizumab as compared with chemotherapy. Table 68 and Figure 8 summarize the efficacy results for KEYNOTE-024.

Table 68: Efficacy Results in KEYNOTE-024

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=154	Chemotherapy n=151
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Median in months (95% CI)†	30.0 (18.3, NR)	14.2 (9.8, 19.0)
Hazard ratio* (95% CI)	0.60 (0.41, 0.89)	
p-Value (stratified log-rank)	0.005‡	
Objective Response Rate		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

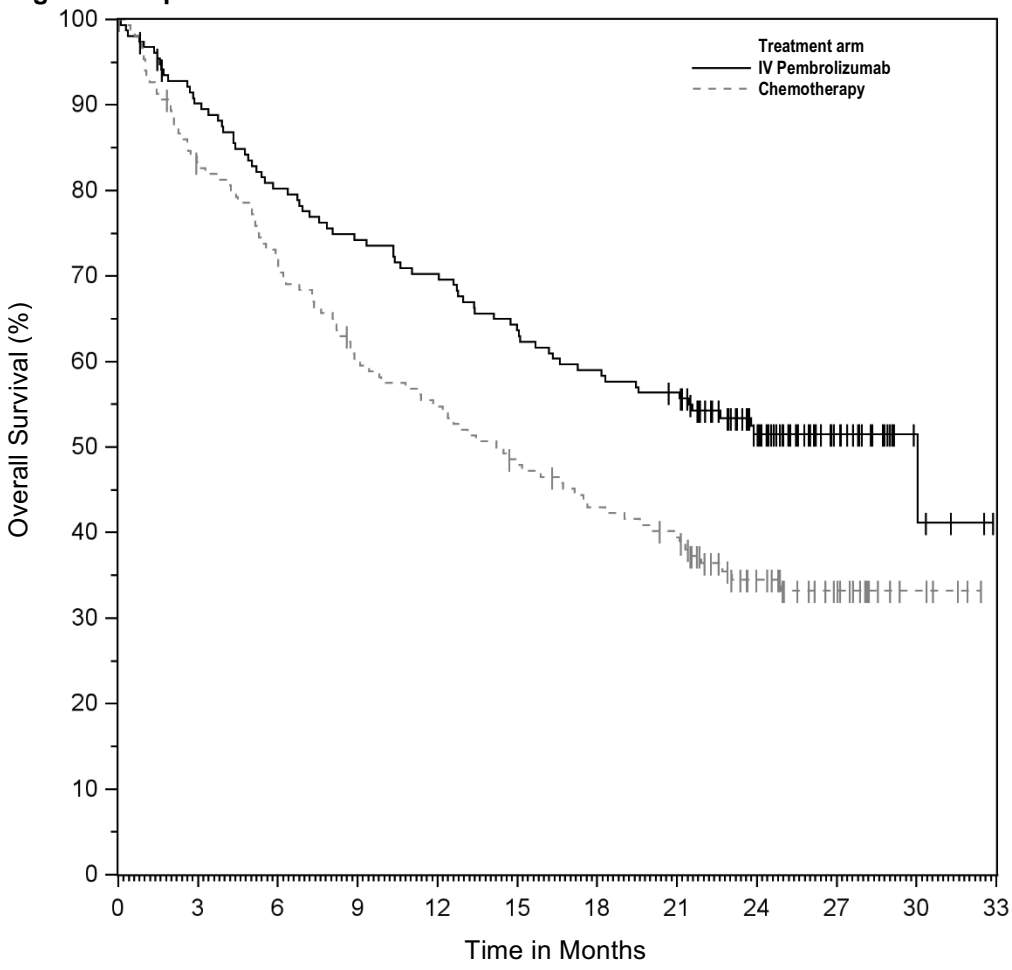
* Based on the stratified Cox proportional hazard model for the interim analysis

† Based on the protocol-specified final OS analysis conducted at 169 events, which occurred 14 months after the interim analysis.

‡ p-Value is compared with 0.0118 of the allocated alpha for the interim analysis

NR = not reached

Figure 8: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024*



Number at Risk												
IV Pembrolizumab	154	136	121	112	106	96	89	83	52	22	5	0
Chemotherapy	151	123	107	88	80	70	61	55	31	16	5	0

*Based on the protocol-specified final OS analysis conducted at 169 events, which occurred 14 months after the interim analysis.

Previously treated NSCLC with PD-L1 expression (TPS ≥1%)

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx assay. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG PS (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive intravenous pembrolizumab 2 mg/kg intravenously every 3 weeks, intravenous pembrolizumab 10 mg/kg intravenously every 3 weeks or docetaxel intravenously 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. Patients randomized to intravenous pembrolizumab were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression. Assessment of tumor status was

performed every 9 weeks. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and DoR in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 69 and 70 and Figure 9 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 69: Efficacy Results of the Subgroup of Patients with TPS ≥50% in KEYNOTE-010

Endpoint	Intravenous Pembrolizumab 2 mg/kg every 3 weeks n=139	Intravenous Pembrolizumab 10 mg/kg every 3 weeks n=151	Docetaxel 75 mg/m^2 every 3 weeks n=152
OS			
Deaths (%)	58 (42%)	60 (40%)	86 (57%)
Median in months (95% CI)	14.9 (10.4, NR)	17.3 (11.8, NR)	8.2 (6.4, 10.7)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	89 (64%)	97 (64%)	118 (78%)
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Objective Response Rate			
ORR† (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 16.8+)	NR (2.1+, 17.8+)	8.1 (2.1+, 8.8+)

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

† All responses were partial responses

NR = not reached

Table 70: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

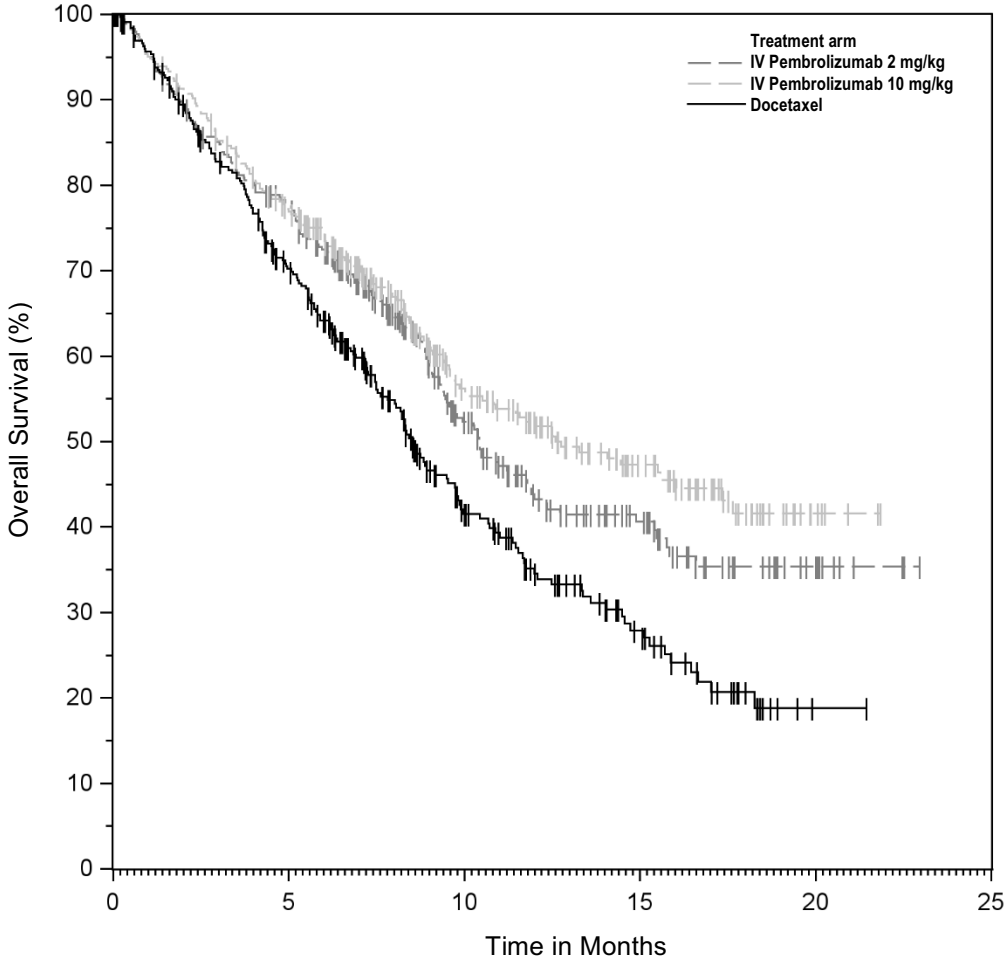
Endpoint	Intravenous Pembrolizumab 2 mg/kg every 3 weeks n=344	Intravenous Pembrolizumab 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	266 (77%)	255 (74%)	257 (75%)
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value (stratified log-rank)	0.068	0.005	---
Objective Response Rate			
ORR† (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

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

† All responses were partial responses

NR = not reached

Figure 9: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-010 (TPS ≥1%)



Number at Risk						
IV Pembrolizumab 2 mg/kg	344	259	115	49	12	0
IV Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

Neoadjuvant and adjuvant treatment of resectable NSCLC

The efficacy of intravenous pembrolizumab in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with intravenous pembrolizumab as a single agent was investigated in KEYNOTE-671 (NCT03425643), a multicenter, randomized, double-blind, placebo-controlled trial conducted in 797 patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition. Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or a history of interstitial lung disease or pneumonitis that required steroids were ineligible. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS ≥50% or <50%), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia).

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

- Treatment Arm A: neoadjuvant intravenous pembrolizumab 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, intravenous pembrolizumab 200 mg was administered every 3 weeks for up to 13 cycles.

- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with intravenous pembrolizumab or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The trial was not designed to isolate the effect of intravenous pembrolizumab in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Additional efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review.

The study population characteristics were: median age of 64 years (range: 26 to 83); 45% age 65 or older and 7% age 75 or older; 71% male; 61% White, 31% Asian, 2% Black, 4% race not reported; 9% Hispanic or Latino; 63% ECOG PS of 0 and 37% ECOG PS of 1. Thirty percent had Stage II and 70% had Stage III disease; 33% had TPS ≥50% and 67% had TPS <50%; 43% had tumors with squamous histology and 57% had tumors with non-squamous histology; 31% were from the East Asian region.

Eighty-one percent of patients in the intravenous pembrolizumab in combination with platinum-containing chemotherapy arm received definitive surgery compared to 76% of patients in the placebo in combination with platinum-containing chemotherapy arm.

The trial demonstrated statistically significant improvements in OS and EFS for patients randomized to intravenous pembrolizumab in combination with platinum-containing chemotherapy followed by intravenous pembrolizumab as a single agent compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone.

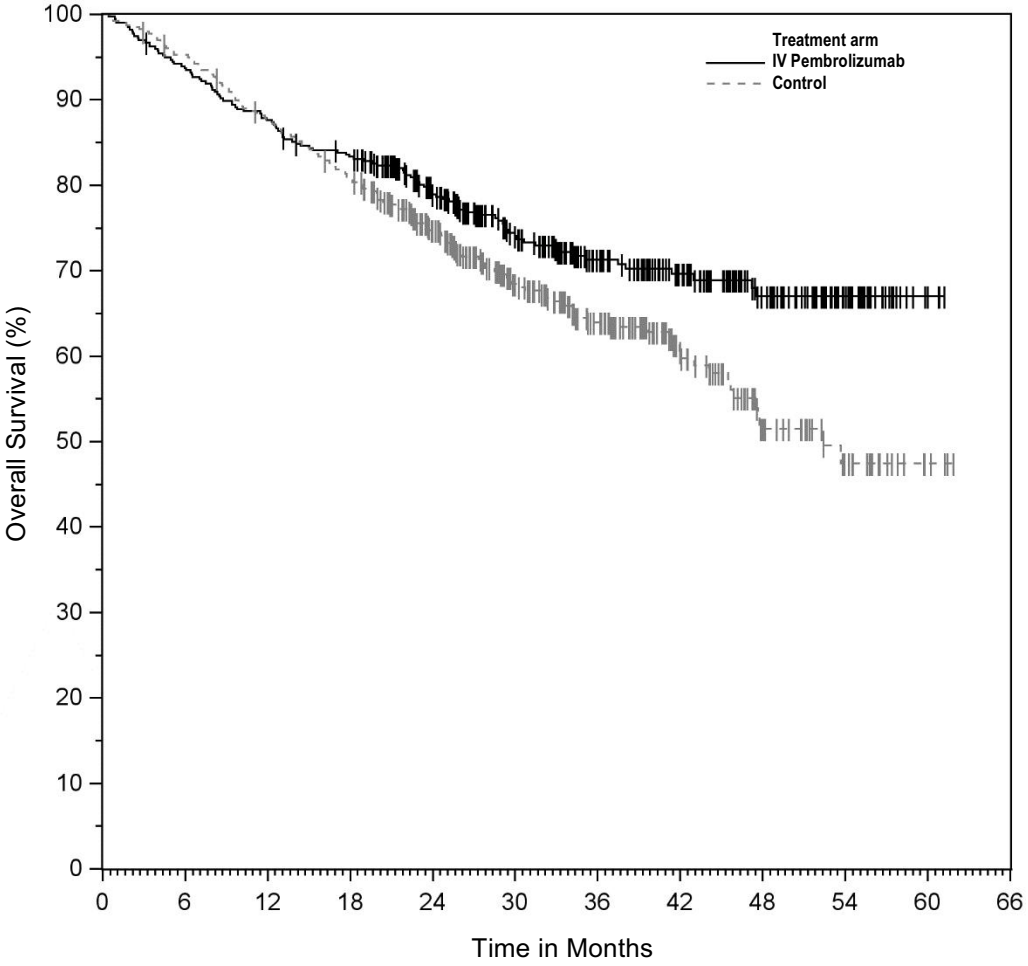
Table 71 and Figure 10 summarize the efficacy results for KEYNOTE-671.

Table 71: Efficacy Results in KEYNOTE-671

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy/Intravenous Pembrolizumab n=397	Placebo with chemotherapy/Placebo n=400
OS		
Number of patients with event (%)	110 (28%)	144 (36%)
Median in months* (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.93)	
p-Value‡,§	0.0103	
EFS		
Number of patients with event (%)	139 (35%)	205 (51%)
Median in months* (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)
Hazard ratio† (95% CI)	0.58 (0.46, 0.72)	
p-Value‡,¶	<0.0001	

* Based on Kaplan-Meier estimates
† Based on Cox regression model with treatment as a covariate stratified by stage, tumor PD-L1 expression, histology, and geographic region
‡ Based on stratified log-rank test
§ Compared to a two-sided p-Value boundary of 0.0109
¶ Compared to a two-sided p-Value boundary of 0.0092
NR = not reached

Figure 10: Kaplan-Meier Curve for Overall Survival in KEYNOTE-671



Number at Risk												
IV Pembrolizumab	397	371	347	327	277	205	148	108	69	32	4	0
Control	400	379	347	319	256	176	125	77	39	20	4	0

The trial demonstrated a statistically significant difference in pCR rate (18.1% vs. 4.0%; p<0.0001) and mPR rate (30.2% vs. 11.0%; p<0.0001).

Adjuvant treatment of resected NSCLC

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-091 (NCT02504372), a multicenter, randomized, triple-blind, placebo-controlled trial conducted in 1177 patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC by AJCC 7th edition. Patients had not received neoadjuvant radiotherapy or chemotherapy. Adjuvant chemotherapy up to 4 cycles was optional. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis. Randomization was stratified by stage (IB vs. II vs. IIIA), receipt of adjuvant chemotherapy (yes vs. no), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS ≥50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive intravenous pembrolizumab 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST v1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity or up to one year. Tumor assessments were conducted every 12 weeks for the first year, then every 6 months for years 2 to 3, and then annually through year 5. After year 5, imaging was performed as per local standard of care. The major efficacy outcome measure was investigator-assessed disease-free survival (DFS). An additional efficacy outcome measure was OS.

Of 1177 patients randomized, 1010 (86%) received adjuvant platinum-based chemotherapy following resection. Among these 1010 patients, the median age was 64 years (range: 35 to 84), 49% age 65 or older; 68% male; 77% White, 18% Asian; 86% current or former smokers; and 39% with ECOG PS of 1. Eleven percent had Stage IB, 57% had Stage II, and 31% had Stage IIIA disease. Thirty-nine percent had PD-L1 TPS <1% [negative], 33% had TPS 1-49%, and 28% had TPS ≥50%. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The trial met its primary endpoint, demonstrating a statistically significant improvement in DFS in the overall population for patients randomized to the intravenous pembrolizumab arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). OS results were not mature with only 42% of pre-specified OS events in the overall population.

Table 72 and Figure 11 summarize the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

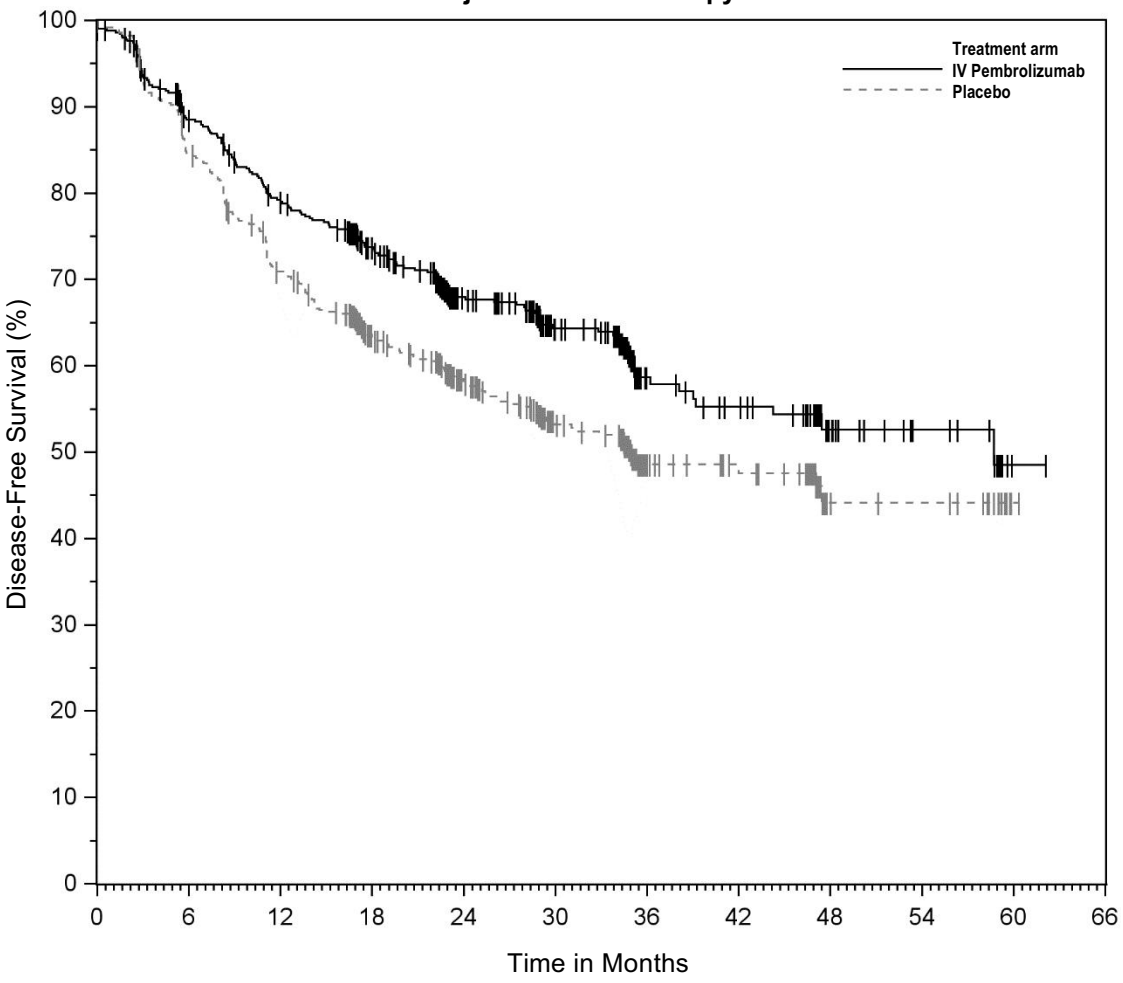
Table 72: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks n=506**	**Placebo n=504**
DFS		
Number (%) of patients with event	177 (35%)	231 (46%)
Median in months (95% CI)	58.7 (39.2, NR)	34.9 (28.6, NR)
Hazard ratio* (95% CI)	0.73 (0.60, 0.89)	

* Based on the unstratified univariate Cox regression model

NR = not reached

Figure 11: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy



Number at Risk												
IV Pembrolizumab	506	422	372	308	227	158	71	61	27	16	1	0
Placebo	504	422	349	272	206	134	58	47	17	15	1	0

14.5 Malignant Pleural Mesothelioma

First-line treatment of unresectable advanced or metastatic malignant pleural mesothelioma (MPM) with pemetrexed and platinum chemotherapy

The efficacy of intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-483 (NCT02784171), a multicenter, randomized, open-label, active-controlled trial that enrolled 440 patients with unresectable advanced or metastatic MPM and 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:

- Intravenous pembrolizumab 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 intravenous pembrolizumab 200 mg every 3 weeks.

- 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 intravenous pembrolizumab 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. The main efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR according to mRECIST.

The study population characteristics were: median age of 70 years (77% age 65 or older); 76% male; 79% White, 21% race not reported or unknown; 2% Hispanic or Latino; and 53% ECOG performance status of 1. Seventy-eight percent had epithelioid and 22% had non-epithelioid histology; 60% had tumors with PD-L1 CPS ≥1 and 30% had tumors with PD-L1 CPS <1.

The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to intravenous pembrolizumab in combination with chemotherapy compared with patients randomized to chemotherapy alone. Table 73 and Figure 12 summarize the efficacy results for KEYNOTE-483.

Table 73: Efficacy Results in KEYNOTE-483

Endpoint	**Intravenous pembrolizumab 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%)
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
Hazard ratio* (95% CI)	0.79 (0.64, 0.98)	
p-Value†	0.0162	
PFS		
Number (%) of patients with event	190 (86%)	166 (76%)
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Hazard ratio* (95% CI)	0.80 (0.65, 0.99)	
p-Value†	0.0194	
Objective Response Rate		
ORR % (95% CI)	52% (45.5, 59.0)	29% (23.0, 35.4)
Complete responses	1 (0.5%)	0 (0%)
Partial responses	115 (52%)	63 (29%)
p-Value‡	<0.00001	
Duration of Response§		
Median in months (95% CI)	6.9 (5.8, 8.3)	6.8 (5.5, 8.5)

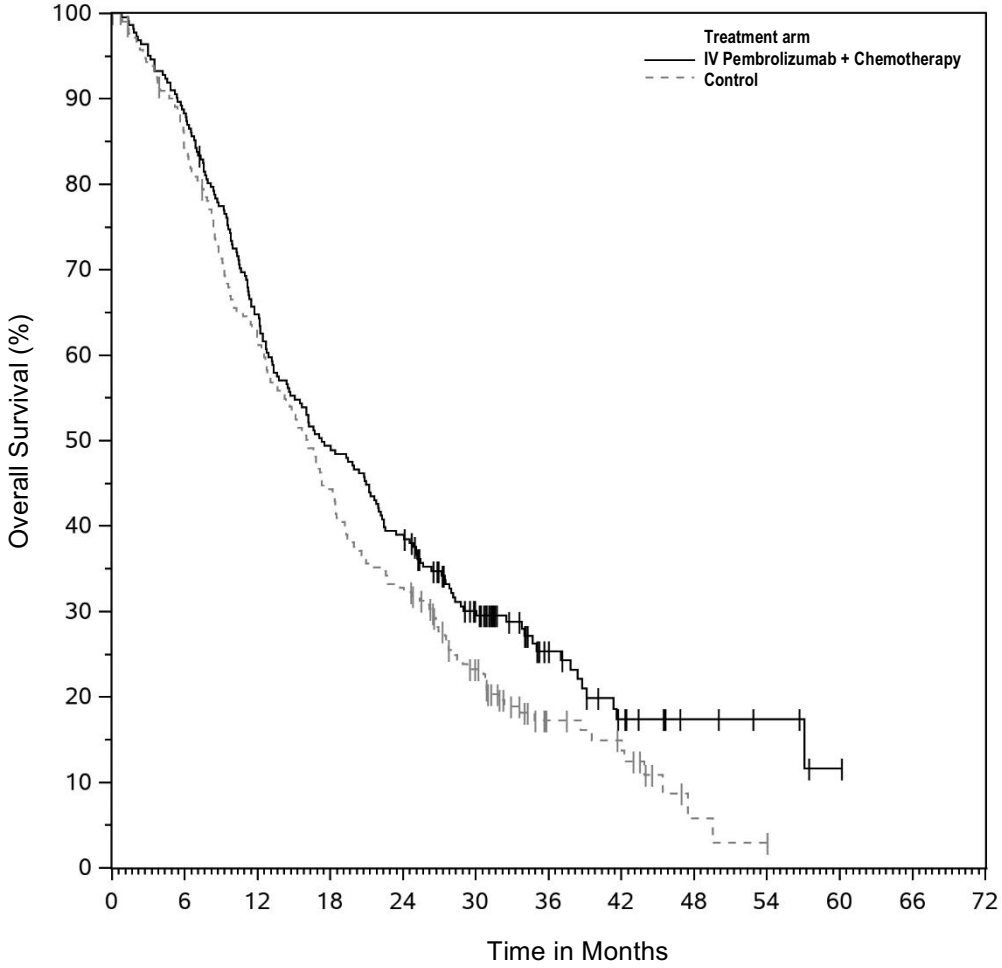
* Based on stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on Miettinen and Nurminen method stratified by histological subtype at randomization (epithelioid vs. non-epithelioid)

§ Based on patients with a best overall response as confirmed complete or partial response; n=116 for patients in the intravenous pembrolizumab combination arm; n=63 for patients in the chemotherapy arm

Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483



Number at Risk													
IV Pembrolizumab + Chemotherapy	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

In a pre-specified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology (n=345), the hazard ratio (HR) for OS was 0.89 (95% CI: 0.70, 1.13), with median OS of 19.8 months in intravenous pembrolizumab in combination with chemotherapy and 18.2 months in chemotherapy alone. In the subgroup of patients with non-epithelioid histology (n=95), the HR for OS was 0.57 (95% CI: 0.36, 0.89), with median OS of 12.3 months in intravenous pembrolizumab in combination with chemotherapy and 8.2 months in chemotherapy alone.

14.6 Head and Neck Squamous Cell Cancer

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC for Tumors Expressing PD-L1 (CPS ≥1)

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-689 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC [AJCC, 8th edition]. Patients with active autoimmune disease requiring 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 assay.

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

- neoadjuvant intravenous pembrolizumab 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, 3 cycles of adjuvant intravenous pembrolizumab 200 mg every 3 weeks in combination with radiotherapy (RT) with or without 3 cycles of cisplatin 100 mg/m^2 every 3 weeks. This was followed by intravenous pembrolizumab 200 mg every 3 weeks for up to 12 cycles.
- no neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m^2 every 3 weeks.

  On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Treatment with intravenous pembrolizumab continued until disease progression by RECIST v1.1 per BICR during the neoadjuvant phase that precluded surgery, local or metastatic recurrence during the adjuvant phase, completion of treatment, 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 with or without 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.

The trial was not designed to isolate the effect of intravenous pembrolizumab in each phase (neoadjuvant or adjuvant) of treatment.

The major 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. Additional efficacy outcome measures were major pathological response (mPR) as assessed by BIPR, and overall survival (OS).

The demographic and baseline 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 or African American, 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. Sixty-eight percent of patients' tumors had PD-L1 expression of CPS ≥10.

Eighty-eight percent of patients received definitive surgery in both the intravenous pembrolizumab and the SOC arm.

Seventy-six percent of patients in the intravenous pembrolizumab arm and 78% of patients in the SOC arm started the radiation phase of treatment. In the intravenous pembrolizumab arm, 35% of patients received intravenous pembrolizumab and cisplatin with concurrent RT, 57% of patients received intravenous pembrolizumab alone with concurrent RT, 3% of patients received cisplatin alone with concurrent RT, 5% of patients received RT alone and one patient (0.4%) received intravenous pembrolizumab alone without concurrent RT. On the SoC arm, 52% of patients received cisplatin with concurrent RT while 48% patients received RT alone.

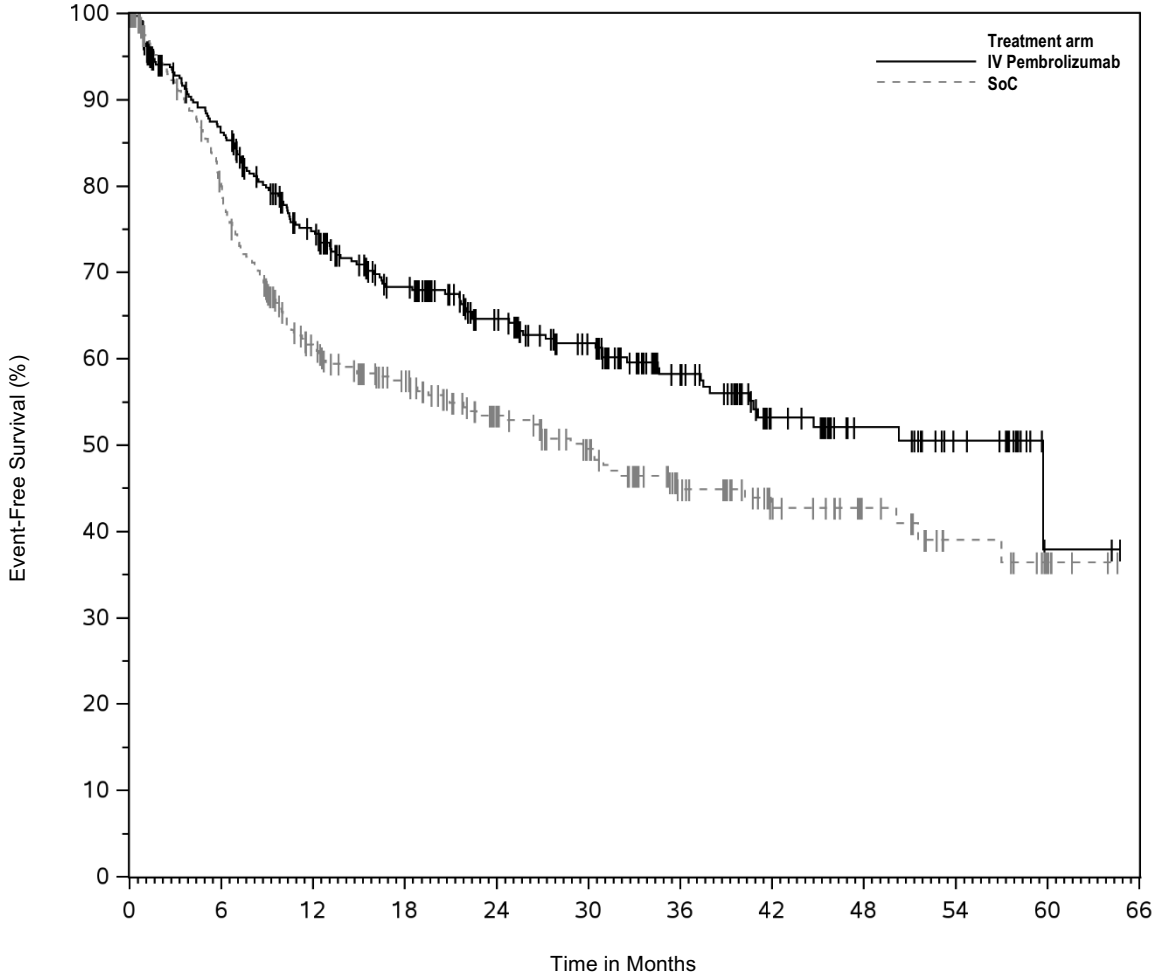
The trial demonstrated a statistically significant improvement in EFS for patients randomized to the intravenous pembrolizumab arm compared to those randomized to the standard of care (SOC) arm at the first pre-specified interim analysis. Table 74 and Figure 13 summarize efficacy results in KEYNOTE-689 for patients with HNSCC CPS ≥1.

Table 74: Efficacy Results for Perioperative Intravenous Pembrolizumab with adjuvant RT with or without cisplatin in Patients with HNSCC CPS ≥1 in KEYNOTE-689

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks with RT with or without cisplatin n=347	RT with or without cisplatin n=335
EFS		
Number of events, n (%)	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	

* 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
NR = not reached

Figure 13: Kaplan-Meier Curve for Event-free Survival for Intravenous Pembrolizumab in Patients with HNSCC CPS ≥1 in KEYNOTE-689



Number at Risk												
IV Pembrolizumab	347	274	220	181	147	122	83	51	33	21	2	0
SoC	335	245	170	140	104	82	56	36	25	15	7	0

While OS results were not mature at this interim analysis, with 76% of pre-specified OS events in the CPS ≥1 population, no trend towards a detriment was observed.

Hypopharyngeal Tumors
In an exploratory subgroup analysis of patients with PD-L1-positive (CPS ≥1) hypopharyngeal tumors who were randomized (n=51), the EFS HR was 2.28 (95% CI: 0.79, 6.56). Among these patients, 23 patients in the intravenous pembrolizumab arm received surgery, of which 17 patients (74%) had R0 resections. On the SOC arm, 23 patients received surgery, of which 20 (87%) had R0 resections.

Oral Cavity, Oropharyngeal and Laryngeal Tumors
In an exploratory subgroup analysis of patients with PD-L1 positive (CPS ≥1) oral cavity, oropharyngeal and laryngeal tumors who received surgery (n=555), 91% of patients on the intravenous pembrolizumab arm had R0 resections while 85% of patients on the SOC arm had R0 resections.

First-line treatment of metastatic or unresectable, recurrent HNSCC

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the PD-L1 IHC 22C3 pharmDx assay, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

- Intravenous pembrolizumab 200 mg intravenously every 3 weeks
- Intravenous pembrolizumab 200 mg intravenously every 3 weeks, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m^2 intravenously every 3 weeks, and FU 1000 mg/m^2/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)
- Cetuximab 400 mg/m^2 intravenously as the initial dose then 250 mg/m^2 intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m^2 intravenously every 3 weeks, and FU 1000 mg/m^2/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)

Treatment with intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of intravenous pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months. A retrospective re-classification of patients' tumor PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx assay was conducted using the tumor specimens used for randomization.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) sequentially tested in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1, and the overall population.

The study population characteristics were: median age of 61 years (range: 20 to 94), 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20.

The trial demonstrated a statistically significant improvement in OS for patients randomized to intravenous pembrolizumab in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. Table 75 and Figure 14 summarize efficacy results for intravenous pembrolizumab in combination with chemotherapy.

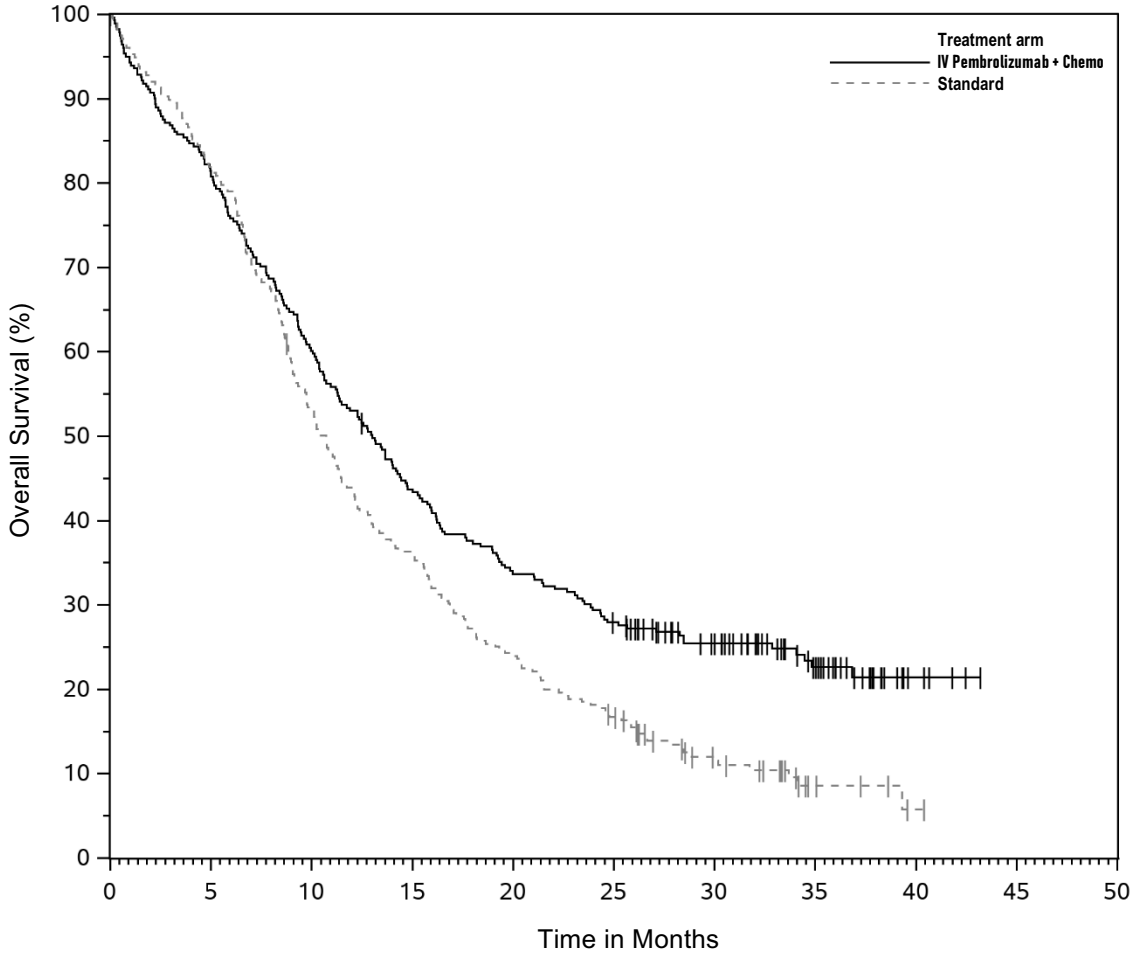
Table 75: Efficacy Results* for Intravenous Pembrolizumab plus Platinum/Fluorouracil in KEYNOTE-048

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks Platinum FU n=281	Cetuximab Platinum FU n=278
OS		
Number (%) of patients with event	197 (70%)	223 (80%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio† (95% CI)	0.77 (0.63, 0.93)	
p-Value‡	0.0067	
PFS		
Number of patients with event (%)	244 (87%)	253 (91%)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
Hazard ratio† (95% CI)	0.92 (0.77, 1.10)	
p-Value‡	0.3394	
Objective Response Rate		
ORR§ (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response rate	6%	3%
Partial response rate	30%	33%
Duration of Response		
Median in months (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)

* Results at a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

At the pre-specified final OS analysis for the ITT population, the hazard ratio was 0.72 (95% CI: 0.60, 0.87). In addition, KEYNOTE-048 demonstrated a statistically significant improvement in OS for the subgroups of patients with PD-L1 CPS ≥1 (HR=0.65, 95% CI: 0.53, 0.80) and CPS ≥20 (HR=0.60, 95% CI: 0.45, 0.82).

Figure 14: Kaplan-Meier Curve for Overall Survival for Intravenous Pembrolizumab plus Platinum/Fluorouracil in KEYNOTE-048*



Number at Risk											
IV Pembrolizumab + Chemo	281	227	169	122	94	77	55	29	5	0	0
Standard	278	227	147	100	66	45	23	6	1	0	0

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

First-line treatment of metastatic or unresectable, recurrent HNSCC for Tumors Expressing PD-L1 (CPS ≥1) as a single agent

The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to intravenous pembrolizumab as a single agent compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis. At the time of the interim and final analyses, there was no significant difference in OS between the intravenous pembrolizumab single agent arm and the control arm for the overall population.

Table 76 summarizes efficacy results for intravenous pembrolizumab as a single agent in the subgroups of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 15 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

Table 76: Efficacy Results* for Intravenous Pembrolizumab as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

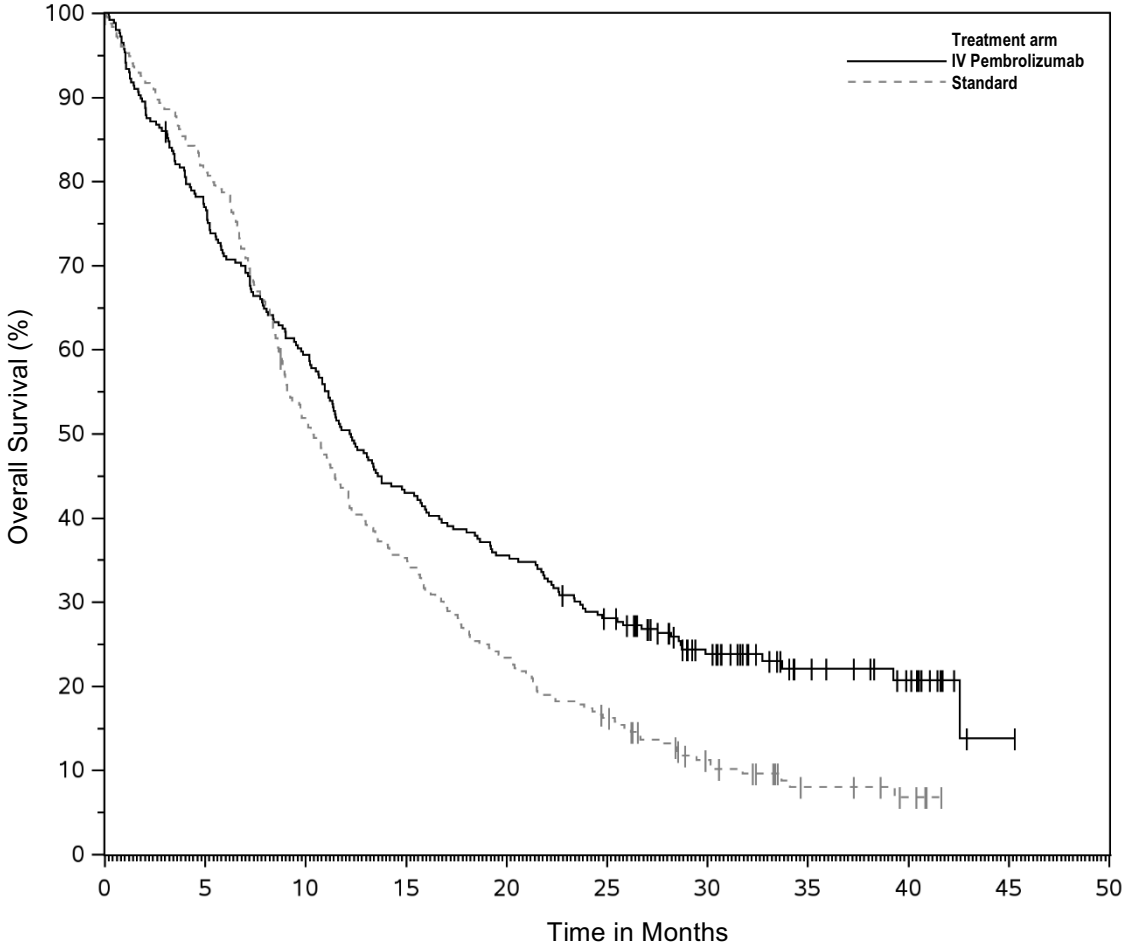
Endpoint	CPS ≥1		CPS ≥20	
	Intravenous Pembrolizumab 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	Intravenous Pembrolizumab 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio† (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value‡	0.0171		0.0015	
PFS				
Number of events (%)	225 (88%)	231 (91%)	113 (85%)	111 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
Hazard ratio† (95% CI)	1.15 (0.95, 1.38)		0.97 (0.74, 1.27)	
Objective Response Rate				
ORR§ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)	23% (16.4, 31.4)	36% (27.6, 45.3)
Complete response rate	5%	3%	8%	3%
Partial response rate	14%	32%	16%	33%
Duration of Response				
Median in months (range)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)	20.9 (2.7, 34.8+)	4.2 (1.2+, 22.3+)

* Results at a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ Based on a stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

At the pre-specified final OS analysis comparing intravenous pembrolizumab as a single agent to cetuximab in combination with chemotherapy, the hazard ratio for the subgroup of patients with CPS ≥1 was 0.74 (95% CI: 0.61, 0.90) and the hazard ratio for the subgroup of patients with CPS ≥20 was 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC at the time of the pre-specified final OS analysis, the median OS was 10.8 months (95% CI: 9.0, 12.6) for intravenous pembrolizumab as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.86 (95% CI: 0.66, 1.12).

Figure 15: Kaplan-Meier Curve for Overall Survival for Intravenous Pembrolizumab as a Single Agent in KEYNOTE-048 (CPS ≥1)*



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

Previously treated recurrent or metastatic HNSCC

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-012 (NCT01848834), a multicenter, non-randomized, open-label, multi-cohort study that enrolled 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS ≥2 were ineligible.

Patients received intravenous pembrolizumab 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

The study population characteristics were median age of 60 years, 32% age 65 or older; 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, the median DoR had not been reached (range: 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and DoR were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

14.7 Urothelial Cancer

In Combination with Enfortumab Vedotin-ejfv for the Treatment of Patients with Urothelial Cancer

The efficacy of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv was evaluated in KEYNOTE-A39 (NCT04223856), an open-label, randomized, multicenter trial that enrolled 886 patients with locally advanced or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded.

Patients were randomized 1:1 to receive either:

- Intravenous pembrolizumab 200 mg over 30 minutes on Day 1 and enfortumab vedotin-ejfv 1.25 mg/kg on Days 1 and 8 of each 21-day cycle. Intravenous pembrolizumab was given approximately 30 minutes after enfortumab vedotin-ejfv. Treatment was continued until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, intravenous pembrolizumab was continued for up to 2 years.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5) on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity for up to 6 cycles.

Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

The median age was 69 years (range: 22 to 91); 77% were male; 67% were White, 22% were Asian, 1% were Black or African American, and 10% were unknown or other; 12% were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (49%), 1 (47%), or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer, including 72% with visceral and 22% with liver metastases, and 5% had locally advanced urothelial cancer. Eighty-five percent of patients had urothelial carcinoma (UC) histology including 6% with UC mixed squamous differentiation and 2% with UC mixed other histologic variants. Forty-six percent of patients were considered cisplatin-ineligible and 54% were considered cisplatin-eligible at time of randomization.

The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.

The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients randomized to intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as compared to platinum-based chemotherapy. Efficacy results were consistent across all stratified patient subgroups.

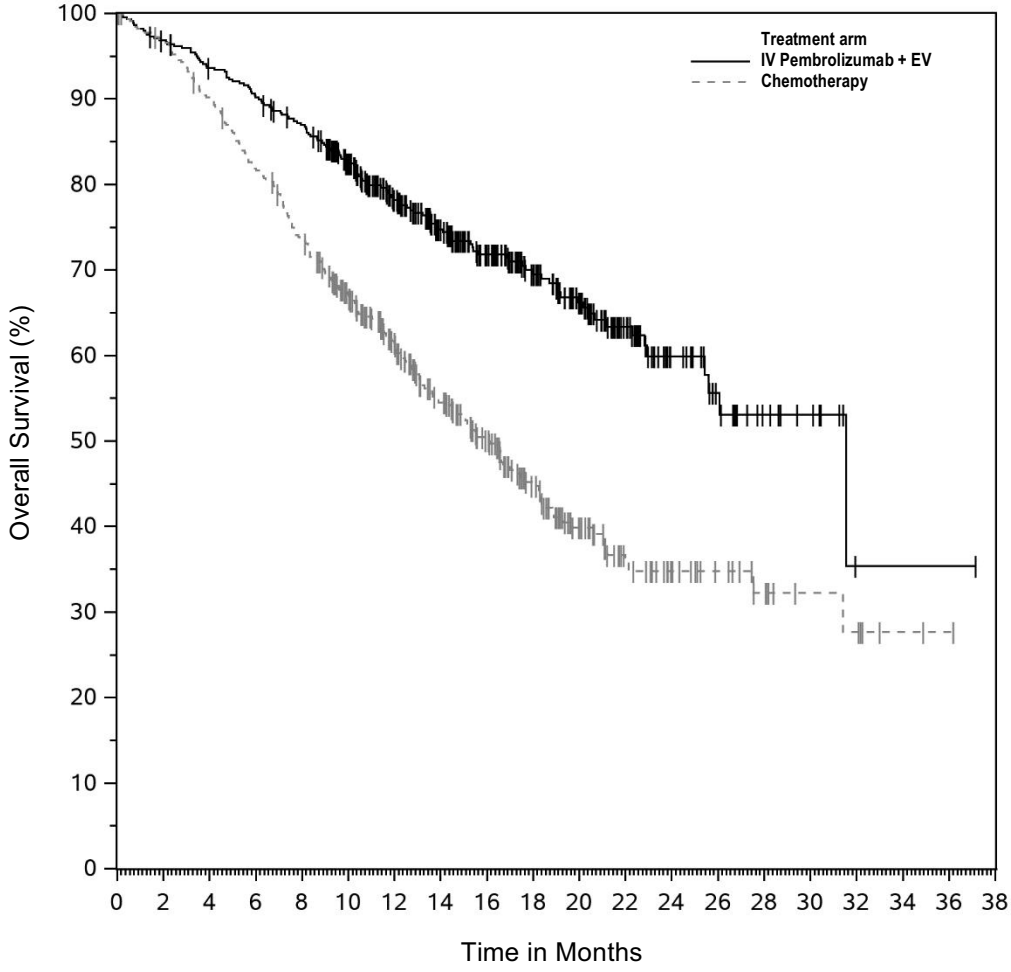
Table 77 and Figures 16 and 17 summarize the efficacy results for KEYNOTE-A39.

Table 77: Efficacy Results in KEYNOTE-A39

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks in combination with Enfortumab Vedotin-ejfv n=442	Cisplatin or Carboplatin with Gemcitabine n=444
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	<0.0001	
Confirmed Objective Response Rate‡		
ORR§ % (95% CI)	68% (63, 72)	44% (40, 49)
p-Value¶	<0.0001	
Complete response	29%	12%
Partial response	39%	32%

* Based on the stratified Cox proportional hazard regression model
† Two-sided p-Value based on stratified log-rank test
‡ Includes only patients with measurable disease at baseline (n=437 for intravenous pembrolizumab in combination with enfortumab vedotin-ejfv, n=441 for chemotherapy).
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases
NR = not reached

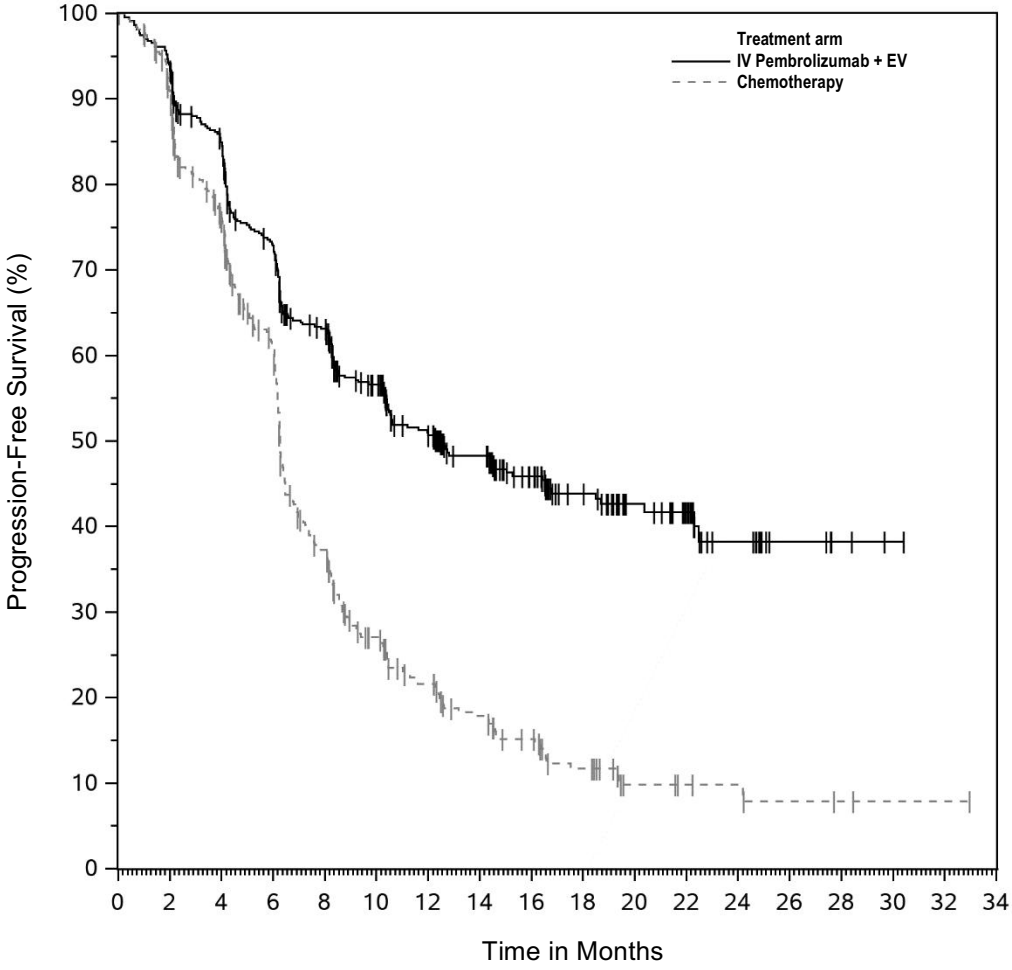
Figure 16: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



Number at Risk

IV Pembrolizumab + EV	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1	0
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1	0

Figure 17: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39



In Combination with Enfortumab Vedotin-ejfv for the Treatment of Patients who are Cisplatin-Ineligible with Urothelial Cancer

The efficacy of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv was evaluated in KEYNOTE-869 (NCT03288545), an open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) study in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-containing chemotherapy *[see Dosage and Administration (2.2)]* and received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received enfortumab vedotin-ejfv 1.25 mg/kg as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by intravenous pembrolizumab 200 mg as an IV infusion on Day 1 of a 21-day cycle approximately 30 minutes after enfortumab vedotin-ejfv. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received intravenous pembrolizumab in combination with enfortumab vedotin-ejfv. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White, 5% were Black, 4% were Asian and 6% were other, unknown or not reported. Ten percent of patients were Hispanic or Latino. Forty-five percent of patients had an ECOG performance status of 1 and 15% had an ECOG

performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. Reasons for cisplatin-ineligibility included: 60% with baseline creatinine clearance of 30-59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss, and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline, including 22% with liver metastases. Thirty-nine percent of patients had TCC histology; 13% had TCC with squamous differentiation, and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1.

The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range: 0.7 to 52.4) and for Cohort K was 14.8 months (range: 0.6 to 26.2).

Efficacy results are presented in Table 78 below.

Table 78: Efficacy Results in KEYNOTE-869, Combined Dose Escalation Cohort, Cohort A, and Cohort K

Endpoint	Intravenous Pembrolizumab in combination with Enfortumab Vedotin-ejfv n=121
Confirmed ORR (95% CI)	68% (58.7, 76.0)
Complete response rate	12%
Partial response rate	55%

The median duration of response for the dose escalation cohort + Cohort A was 22.1 months (range: 1.0+ to 46.3+) and for Cohort K was not reached (range: 1.2 to 24.1+).

Patients who are Platinum-Ineligible with Urothelial Carcinoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who had one or more comorbidities, including patients who were not eligible for any platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received intravenous pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 74 years; 77% male; and 89% White. Eighty-seven percent had M1 disease, and 13% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Fifty percent of patients had baseline creatinine clearance of <60 mL/min, 32% had ECOG PS of 2, 9% had ECOG PS of 2 and baseline creatinine clearance of <60 mL/min, and 9% had one or more of Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss. Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

The median follow-up time for 370 patients treated with intravenous pembrolizumab was 11.4 months (range: 0.1 to 63.8 months). Efficacy results are summarized in Table 79.

Table 79: Efficacy Results in KEYNOTE-052

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks
	All Subjects n=370
Objective Response Rate	
ORR (95% CI)	29% (24, 34)
Complete response rate	10%
Partial response rate	20%
Duration of Response	
Median in months (range)	33.4 (1.4+, 60.7+)

\+ Denotes ongoing response

Platinum-Eligible Patients with Previously Untreated Urothelial Carcinoma

The efficacy of intravenous pembrolizumab for the first-line treatment of platinum-eligible patients with locally advanced or metastatic urothelial carcinoma was investigated in KEYNOTE-361 (NCT02853305), a multicenter, randomized, open-label, active-controlled study in 1010 previously untreated patients. The safety and efficacy of intravenous pembrolizumab in combination with platinum-based chemotherapy for previously untreated patients with locally advanced or metastatic urothelial carcinoma has not been established.

The study compared intravenous pembrolizumab with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. Among the patients receiving intravenous pembrolizumab plus platinum-based chemotherapy, 44% received cisplatin and 56% received carboplatin.

The study did not meet its major efficacy outcome measures of improved PFS or OS in the intravenous pembrolizumab plus chemotherapy arm compared to the chemotherapy-alone arm. Additional efficacy endpoints, including improvement of OS in the intravenous pembrolizumab monotherapy arm, could not be formally tested.

Previously Treated Urothelial Carcinoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-045 (NCT02256436), a multicenter, randomized (1:1), active-controlled trial in 542 patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either intravenous pembrolizumab 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=90), docetaxel 75 mg/m^2 (n=92), or vinflunine 320 mg/m^2 (n=90). Treatment continued until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age of 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG PS of 0 and 56% ECOG PS of 1; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumor in the lower tract and 14% had a primary

tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

The study demonstrated statistically significant improvements in OS and ORR for patients randomized to intravenous pembrolizumab as compared to chemotherapy. There was no statistically significant difference between intravenous pembrolizumab and chemotherapy with respect to PFS. The median follow-up time for this trial was 9.0 months (range: 0.2 to 20.8 months). Table 80 and Figure 18 summarize the efficacy results for KEYNOTE-045.

Table 80: Efficacy Results in KEYNOTE-045

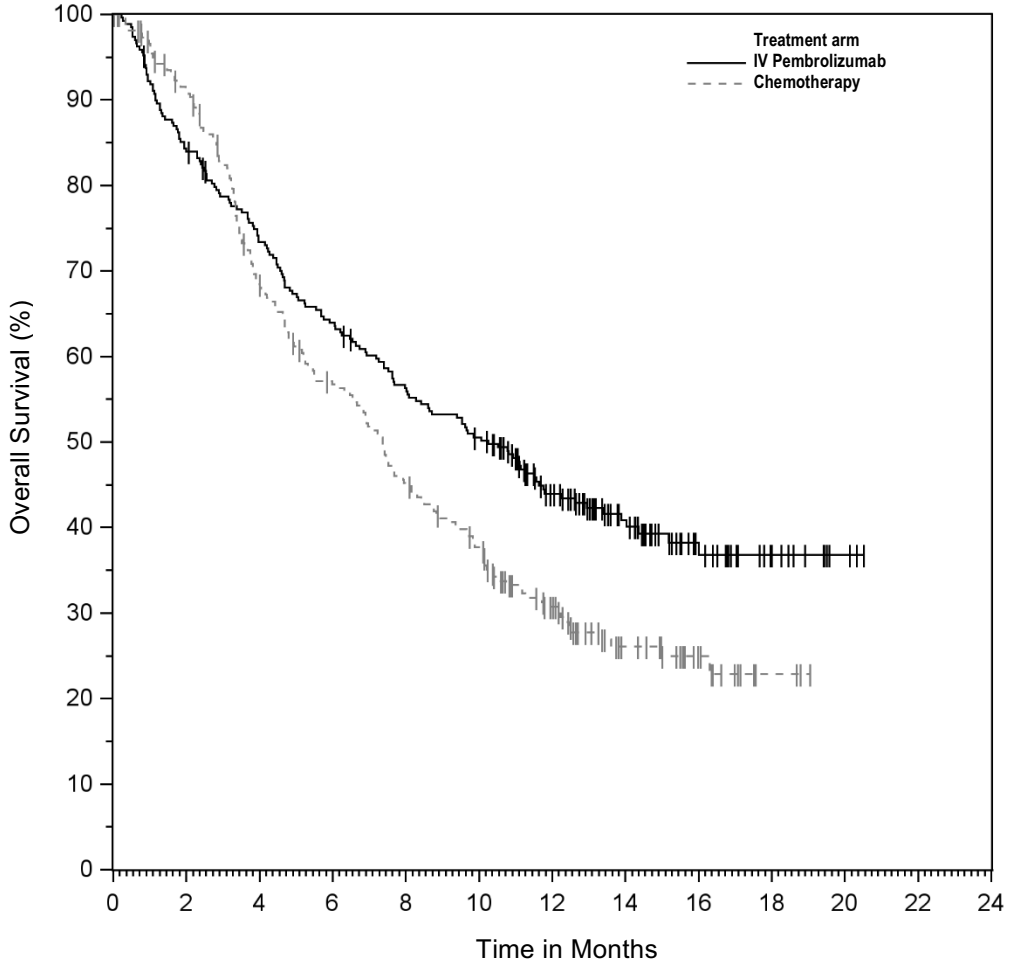
	Intravenous Pembrolizumab 200 mg every 3 weeks n=270	**Chemotherapy n=272**
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value (stratified log-rank)	0.833	
Objective Response Rate		
ORR (95% CI)	21% (16, 27)	11% (8, 16)
Complete response rate	7%	3%
Partial response rate	14%	8%
p-Value (Miettinen-Nurminen)	0.002	
Median duration of response in months (range)	NR (1.6+, 15.6+)	4.3 (1.4+, 15.4+)

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

\+ Denotes ongoing response

NR = not reached

Figure 18: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



Number at Risk													
IV Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

Neoadjuvant and Adjuvant Treatment of Patients Who are Cisplatin-Eligible with MIBC in Combination with Enfortumab Vedotin-ejfv

The efficacy of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as neoadjuvant treatment and continued after radical cystectomy (RC) as adjuvant treatment was investigated in KEYNOTE-B15 (NCT04700124), an open-label, randomized, multicenter, active-controlled trial in patients with previously untreated MIBC with predominant urothelial carcinoma histology and who were candidates for RC with pelvic lymph node dissection (PLND) and were eligible for cisplatin-based chemotherapy. The study excluded patients with primary non-bladder urothelial cancer (i.e., cancer of the ureter, urethra, or renal pelvis) and those with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression.

Randomization was stratified by tumor stage (T2N0 vs. T3/T4aN0 vs. T1-T4aN1), PD-L1 combined positive score (CPS ≥10 vs. CPS <10), and geographic region (United States vs. European Union vs. Rest of World).

Patients were randomized 1:1 to receive either:

- Neoadjuvant intravenous pembrolizumab 200 mg intravenously on Day 1 and enfortumab vedotin-ejfv 1.25 mg/kg intravenously on Days 1 and 8 of each 21-day cycle for 4 cycles prior to surgery, followed

by adjuvant intravenous pembrolizumab 200 mg on Day 1 of each 21-day cycle for 13 cycles and adjuvant enfortumab vedotin-ejfv 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 5 cycles (n=405) or

- Neoadjuvant gemcitabine 1000 mg/m^2 on Days 1 and 8 and cisplatin 70 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles prior to surgery, followed by observation (n=403).

Treatment continued until completion of study medications, disease progression, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumor status, including CT/MRI, was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-RC. Following RC and PLND, assessment of tumor status, including cystoscopy and urine cytology for patients who did not undergo surgery, was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The study population characteristics were: median age of 66 years (range: 35 to 85 years); 81% male; 80% White, 17% Asian, 1.4% Multiple, 1.2% Black or African American, 0.6% American Indian or Alaska Native, and 0.2% missing; 90% not Hispanic or Latino, 8% Hispanic or Latino, and 1.7% ethnicity unknown/not reported. Seventy-eight percent had ECOG PS of 0 and 22% had ECOG PS of 1; 19%, were T2N0, 73% T3/T4aN0, and 8% T1-T4aN1. Eighty-nine percent of patients had pure urothelial carcinoma histology; 4.8% had urothelial carcinoma with squamous differentiation, 2.6% had urothelial carcinoma with glandular differentiation, and 3.1% had urothelial carcinoma with other variant histology.

A total of 351 (87%) patients in the intravenous pembrolizumab in combination with enfortumab vedotin-ejfv arm and 361 (90%) patients in the gemcitabine with cisplatin arm underwent RC and PLND. A total of 25 (6%) of patients in the gemcitabine with cisplatin arm received adjuvant nivolumab.

The trial was not designed to isolate the effect of intravenous pembrolizumab in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) as assessed by BICR. Overall survival (OS) and pathological complete response (pCR) rate as assessed by blinded independent pathology review were additional efficacy outcome measures.

The trial demonstrated a statistically significant improvement in EFS and OS in patients treated with neoadjuvant and adjuvant intravenous pembrolizumab in combination with enfortumab vedotin-ejfv compared with neoadjuvant gemcitabine with cisplatin. Table 81 and Figures 19 and 20 summarize key efficacy measures.

Table 81: Efficacy Results for Perioperative Intravenous Pembrolizumab with Enfortumab Vedotin-ejfv in KEYNOTE-B15

Endpoint	Perioperative Intravenous Pembrolizumab 200 mg every 3 weeks in combination with Enfortumab Vedotin-ejfv n=405	Neoadjuvant Gemcitabine with Cisplatin n=403
EFS		
Number of patients with event (%)	87 (21%)	146 (36%)
Median in months* (95% CI)	NR (NR, NR)	48.5 (43.3, NR)
Hazard ratio† (95% CI)	0.53 (0.41, 0.70)	
p-Value‡	<0.0001	
OS		
Number of patients with event (%)	69 (17%)	99 (25%)
Median in months* (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio† (95% CI)	0.65 (0.48, 0.89)	
p-Value‡	0.0029	

NR = not reached

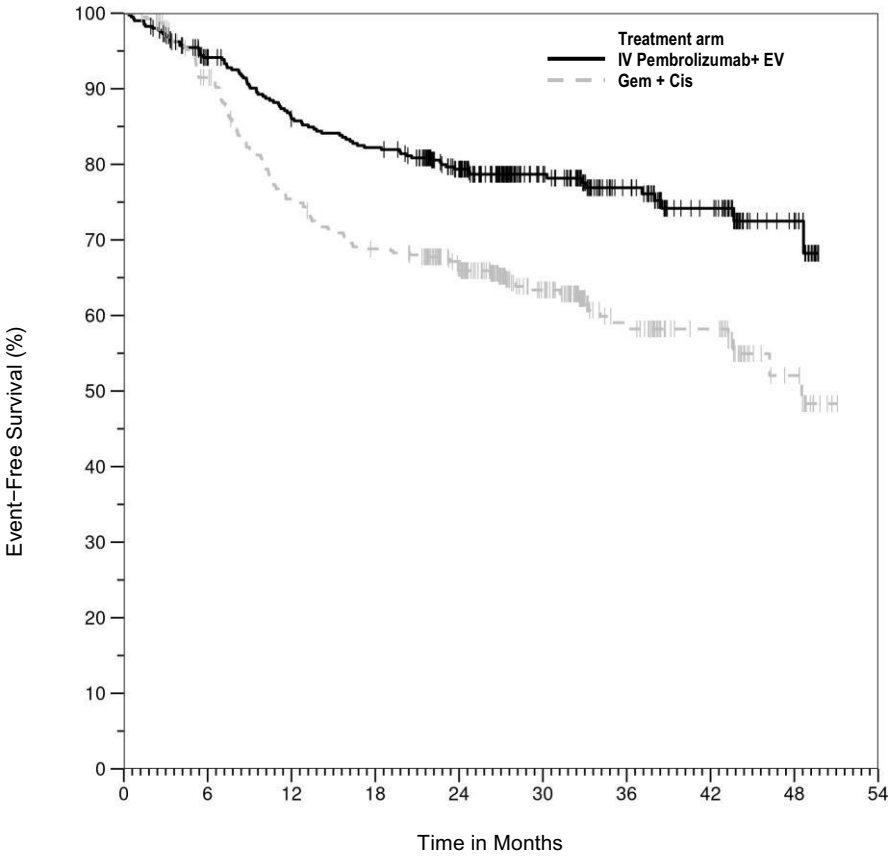
EFS is defined as time from randomization to the first of: disease progression preventing curative surgery, failure to undergo surgery for participants with muscle invasive residual disease, incomplete surgical resection, local or distant recurrence after surgery, or death.

* Based on Kaplan-Meier estimates

† Based on stratified Cox regression model with Efron's method of tie handling with treatment as a covariate

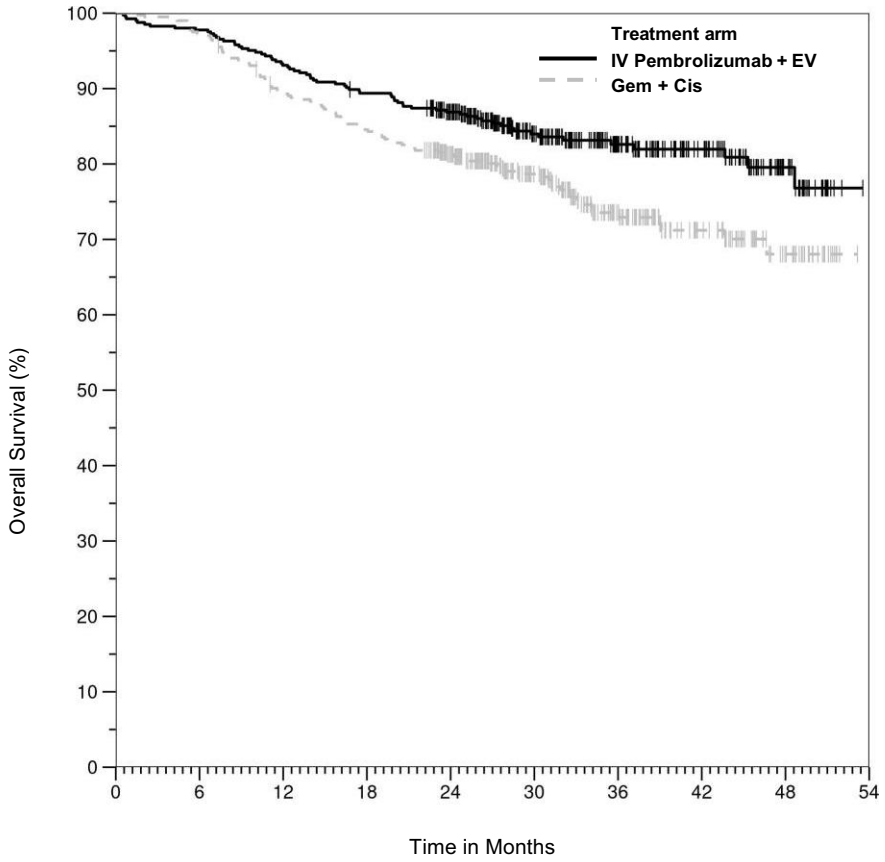
‡ One-sided p-value based on stratified log-rank test

Figure 19: Kaplan-Meier Curve for Event-Free Survival in KEYNOTE-B15



Number at Risk										
IV Pembrolizumab + EV	405	351	317	303	257	154	100	63	23	0
Gem + Cis	403	350	286	259	216	131	70	45	16	0

Figure 20: Kaplan-Meier Curve for Overall Survival in KEYNOTE-B15



Number at Risk										
IV Pembrolizumab + EV	405	396	377	361	325	215	142	90	34	0
Gem + Cis	403	392	358	338	295	201	119	67	29	0

The trial demonstrated a statistically significant difference in pCR rate (55.8% [95% CI: 50.8, 60.7] vs. 32.5% [95% CI: 28.0, 37.3]; p<0.0001).

Neoadjuvant and Adjuvant Treatment of Patients who are Cisplatin-Ineligible with MIBC in Combination with Enfortumab Vedotin-ejfv

The efficacy of intravenous pembrolizumab in combination with enfortumab vedotin-ejfv as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment was investigated in KEYNOTE-905 (NCT03924895), an open-label, randomized, multicenter, active-controlled trial in patients with previously untreated MIBC with predominant urothelial carcinoma histology and who were candidates for radical cystectomy (RC) with pelvic lymph node dissection (PLND) but were ineligible for or declined cisplatin-based chemotherapy. The study excluded patients with primary non-bladder urothelial cancer (i.e., cancer of the ureter, urethra, or renal pelvis) and those with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression.

Randomization was stratified by tumor stage (T2N0 vs. T3/T4aN0 vs. T1-T4aN1), cisplatin-eligibility (cisplatin-ineligible vs. cisplatin-eligible but declined), and geographic region (United States vs. European Union vs. Rest of World).

Patients were randomized 1:1 to receive:

- Neoadjuvant intravenous pembrolizumab 200 mg intravenously on Day 1 and enfortumab vedotin-ejfv 1.25 mg/kg intravenously on Days 1 and 8 of each 21-day cycle for 3 cycles prior to surgery, followed by adjuvant intravenous pembrolizumab 200 mg over 30 minutes on Day 1 of each 21-day cycle for 14 cycles and adjuvant enfortumab vedotin-ejfv 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 6 cycles (n=170).
- Immediate RC and PLND alone (n=174).

Treatment continued until completion of study medications, disease progression, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumor status, including CT/MRI, was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-radical cystectomy. Following RC and PLND, assessment of tumor status, including cystoscopy and urine cytology for patients who did not undergo surgery, was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The study population characteristics were: median age of 73 years (range: 46 to 87 years); 78% male; 78% White, 16% Asian, 3.2% Multiple, 1.2% Black or African American, 0.3% American Indian or Alaska Native, and 1.2% missing; 6% Hispanic or Latino, 91% not Hispanic or Latino, and 2.9% not reported; 57% had ECOG PS of 0, 29% had ECOG PS of 1, and 14% had ECOG PS of 2; 18% were T2N0, 77% T3/T4aN0, and 4.9% T1-T4aN1. Ninety-one percent of patients had pure urothelial carcinoma histology; 4.4% had urothelial carcinoma with squamous differentiation, 2.6% had urothelial carcinoma with glandular differentiation, and 2% had urothelial carcinoma with other variant histology. Among the 281 patients who were ineligible for cisplatin, 72% had baseline creatinine clearance of 30-59 mL/min, 17% had ECOG PS of 2, 21% had Grade 2 or greater hearing loss, 3.9% had New York Heart Association Class III heart failure, and 13% met more than one cisplatin-ineligibility criterion.

A total of 149 (88%) patients in the intravenous pembrolizumab in combination with enfortumab vedotin-ejfv arm and 156 (90%) patients in the RC and PLND alone arm underwent RC and PLND. A total of 29 (17%) of patients in the RC and PLND alone arm received adjuvant nivolumab.

The trial was not designed to isolate the effect of intravenous pembrolizumab in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was EFS as assessed by BICR. Overall survival (OS) and pathological complete response (pCR) rate as assessed by blinded independent pathology review were additional efficacy outcome measures.

The trial demonstrated a statistically significant improvement in EFS and OS in patients treated with neoadjuvant and adjuvant intravenous pembrolizumab in combination with enfortumab vedotin-ejfv compared with RC and PLND alone. Table 82 and Figures 21 and 22 summarize key efficacy measures.

Table 82: Efficacy Results for Perioperative Intravenous Pembrolizumab with Enfortumab Vedotin-ejfv in KEYNOTE-905

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks in combination with enfortumab vedotin-ejfv before and after RC with PLND n=170	RC with PLND alone n=174
EFS		
Number of patients with event (%)	48 (28%)	95 (55%)
Median in months* (95% CI)	NR (37.3, NR)	15.7 (10.3, 20.5)
Hazard ratio† (95% CI)	0.40 (0.28, 0.57)	
p-Value‡	<0.0001	
OS		
Number of patients with event (%)	38 (22%)	68 (39%)
Median in months* (95% CI)	NR (NR, NR)	41.7 (31.8, NR)
Hazard ratio† (95% CI)	0.50 (0.33, 0.74)	
p-Value‡	0.0002	

NR = not reached

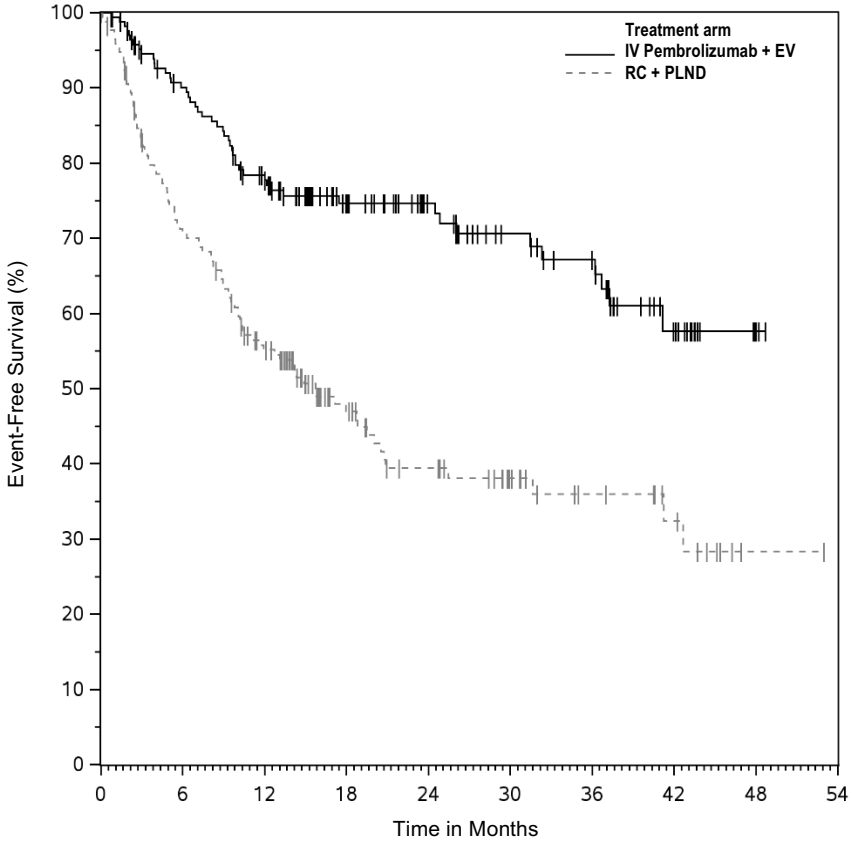
EFS is defined as time from randomization to the first of: disease progression preventing curative surgery, failure to undergo surgery for participants with muscle invasive residual disease, incomplete surgical resection, local or distant recurrence after surgery, or death.

* Based on Kaplan-Meier estimates

† Based on stratified Cox regression model with Efron's method of tie handling with treatment as a covariate

‡ Based on stratified log-rank test

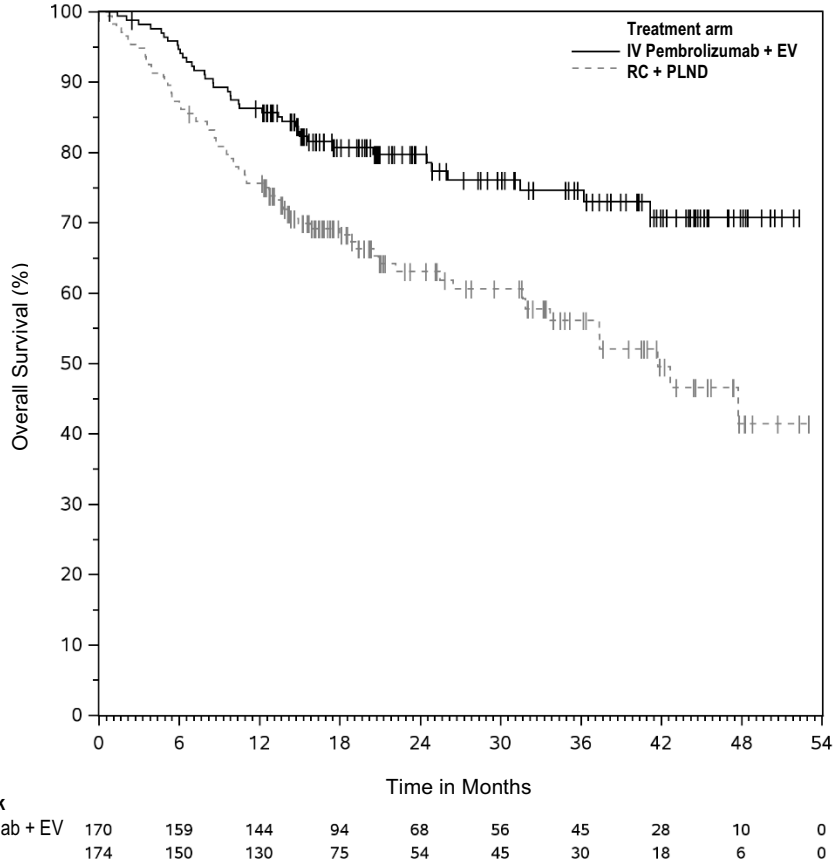
Figure 21: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-905



Number at Risk

IV Pembrolizumab + EV	170	140	116	73	56	42	35	16	3	0
RC + PLND	174	116	84	48	33	22	14	9	1	0

Figure 22: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-905



The trial demonstrated a statistically significant difference in pCR rate (57.1% [95% CI: 49.3, 64.6] vs. 8.6% [95% CI: 4.9, 13.8]; p<0.0001).

BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-057 (NCT02625961), a multicenter, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC was defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy was defined as administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all patients had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, or autoimmune disease or a medical condition that required immunosuppression.

Patients received intravenous pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumor status was performed every 12 weeks for two years and then every 24 weeks for three years, and patients without disease progression could be treated for up to 24 months. The major efficacy outcome measures were

complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response.

The study population characteristics were: median age of 73 years (range: 44 to 92); 44% age ≥75; 84% male; 67% White; and 73% and 27% with an ECOG performance status of 0 or 1, respectively. Tumor pattern at study entry was CIS with T1 (13%), CIS with high grade TA (25%), and CIS (63%). Baseline high-risk NMIBC disease status was 27% persistent and 73% recurrent. The median number of prior instillations of BCG was 12.

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarized in Table 83.

Table 83: Efficacy Results in KEYNOTE-057

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=96
Complete Response Rate (95% CI)	41% (31, 51)
Duration of Response*	
Median in months (range)	16.2 (0.0+, 30.4+)
% (n) with duration ≥12 months	46% (18)

* Based on patients (n=39) that achieved a complete response; reflects period from the time complete response was achieved

\+ Denotes ongoing response

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of intravenous pembrolizumab was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.

- KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.
- KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).
- KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.

Adult patients received intravenous pembrolizumab 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051.

In KEYNOTE-164 and KEYNOTE-158, the study population characteristics were median age of 60 years, 36% age 65 or older; 44% male; 78% White, 14% Asian, 4% American Indian or Alaska Native, and 3% Black; and 45% ECOG PS of 0 and 55% ECOG PS of 1. Ninety-two percent of patients had metastatic disease and 4% had locally advanced, unresectable disease. Thirty-seven percent of patients received one prior line of therapy and 61% received two or more prior lines of therapy.

In KEYNOTE-051, the study population characteristics were median age of 11 years (range: 3 to 16); 71% female; 86% White and 14% Asian; and 57% had a Lansky/Karnofsky Score of 100.

Seventy-one percent of patients had Stage IV and 14% had Stage III disease. Fifty-seven percent of patients received one prior line of therapy and 29% received two prior lines of therapy.

Discordant results were observed between local MSI-H or dMMR tests and central testing among patients enrolled in Cohort K of KEYNOTE-158. Among 104 tumor samples that were MSI-H or dMMR by local testing and also tested using the FoundationOne®CDx (F1CDx) test, 59 (56.7%) were MSI-H and 45 (43.3%) were not MSI-H. Among 169 tumor samples that were MSI-H or dMMR by local testing and also tested using the VENTANA MMR RxDx Panel, 105 (62.1%) were dMMR and 64 (37.9%) were pMMR.

Efficacy results are summarized in Tables 84 and 85.

Table 84: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	Intravenous Pembrolizumab n=504*
Objective Response Rate	
ORR (95% CI)†	33.3% (29.2, 37.6)
Complete response rate	10.3%
Partial response rate	23.0%
Duration of Response	n=168
Median in months (range)	63.2 (1.9+, 63.9+)
% with duration ≥12 months	77%
% with duration ≥36 months	39%

* Median follow-up time of 20.1 months (range 0.1 to 71.4 months)
† Of the 7 pediatric patients from KEYNOTE-051, 1 patient had a radiographic complete response after initial growth of their tumor but is not reflected in the results.
\+ Denotes ongoing response

Table 85: Response by Tumor Type

	N	Objective Response Rate n (%)	Objective Response Rate 95% CI	Duration of Response range (months)
CRC	124	42 (34%)	(26%, 43%)	(4.4, 58.5+)
Non-CRC*	380	126 (33%)	(28%, 38%)	(1.9+, 63.9+)
Endometrial cancer	94	47 (50%)	(40%, 61%)	(2.9, 63.2)
Gastric or GE junction cancer	51	20 (39%)	(26%, 54%)	(1.9+, 63.0+)
Small intestinal cancer	27	16 (59%)	(39%, 78%)	(3.7+, 57.3+)
Brain cancer	27†	1 (4%)‡	(0%, 19%)	18.9
Ovarian cancer	25	8 (32%)	(15%, 54%)	(4.2, 56.6+)
Biliary cancer	22	9 (41%)	(21%, 64%)	(6.2, 49.0+)
Pancreatic cancer	22	4 (18%)	(5%, 40%)	(8.1, 24.3+)
Sarcoma	14	3 (21%)	(5%, 51%)	(35.4+, 57.2+)
Breast cancer	13	1 (8%)	(0%,36%)	24.3+
Other§	13	4 (31%)	(9%, 61%)	(6.2+, 32.3+)
Cervical cancer	11	1 (9%)	(0%, 41%)	63.9+
Neuroendocrine cancer	11	1 (9%)	(0%, 41%)	13.3
Prostate cancer	8	1 (13%)	(0%, 53%)	24.5+
Adrenocortical cancer	7	1 (14%)	(0%, 58%)	4.2
Mesothelioma	7	0 (0%)	(0%, 41%)	
Thyroid cancer	7	1 (14%)	(0%, 58%)	8.2
Small cell lung cancer	6	2 (33%)	(4%, 78%)	(20.0, 47.5)
Bladder cancer	6	3 (50%)	(12%, 88%)	(35.6+, 57.5+)
Salivary cancer	5	2 (40%)	(5%, 85%)	(42.6+, 57.8+)
Renal cell cancer	4	1 (25%)	(0%, 81%)	22.0

* Results include patients in Cohort K of KEYNOTE-158 that were later determined to be pMMR or not MSI-H by central testing
† Includes 6 pediatric patients with brain cancer
‡ In addition to the 1 adult responder, 1 pediatric patient had a radiographic complete response after initial growth of their tumor.
§ Includes tumor type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1). Includes 1 pediatric patient with abdominal adenocarcinoma.
\+ Denotes ongoing response

Exploratory analysis by TMB

In an exploratory analysis performed in 138 patients (Cohort K of KEYNOTE-158) who were tested retrospectively for tumor mutation burden (TMB) using an FDA-authorized test, 45 (33%) had tumors with TMB score of <10 mut/Mb; ORR in these 45 patients was 6.7% (95% CI: 1.4, 18.3). Among the 45 patients with TMB score of <10 mut/Mb, 39 of the patients were pMMR/not MSI-H when tested using an FDA-authorized test.

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive intravenous pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 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 intravenous pembrolizumab or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with intravenous pembrolizumab 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 intravenous pembrolizumab at the time of disease progression. The main efficacy outcome measures were PFS (as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Additional efficacy outcome measures were ORR and DoR.

A total of 307 patients were enrolled and randomized to intravenous pembrolizumab (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1; and 27% received prior adjuvant or neoadjuvant chemotherapy. Among 154 patients randomized to receive chemotherapy,143 received chemotherapy per the protocol. Of the 143 patients, 56% received mFOLFOX6, 44% received FOLFIRI, 70% received bevacizumab plus mFOLFOX6 or FOLFIRI, and 11% received cetuximab plus mFOLFOX6 or FOLFIRI.

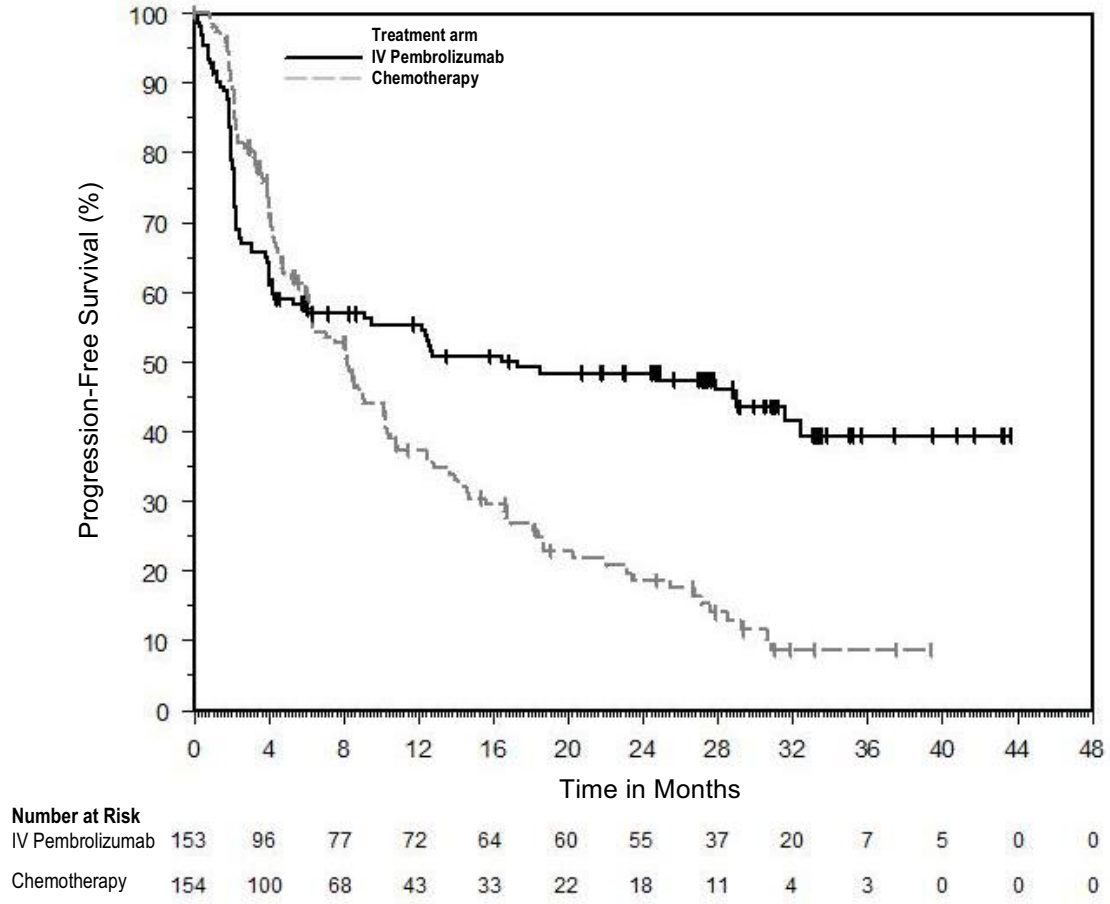
The trial demonstrated a statistically significant improvement in PFS for patients randomized to intravenous pembrolizumab compared with chemotherapy. There was no statistically significant difference between intravenous pembrolizumab and chemotherapy in the final OS analysis. Sixty percent of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including intravenous pembrolizumab. The median follow-up time at the final analysis was 38.1 months (range: 0.2 to 58.7 months). Table 86 and Figure 23 summarize the key efficacy measures for KEYNOTE-177.

Table 86: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
OS‡		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio* (95% CI)	0.74 (0.53, 1.03)	
p-Value§	0.0718	
Objective Response Rate¶		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Duration of Response¶,#		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 monthsᵖ	75%	37%
% with duration ≥24 monthsᵖ	43%	18%

* Based on Cox regression model
† Two-sided p-Value based on log-rank test (compared to a significance level of 0.0234)
‡ Final OS analysis
§ Two-sided p-Value based on log-rank test (compared to a significance level of 0.0492)
¶ Based on confirmed response by BICR review
# Based on n=67 patients with a response in the intravenous pembrolizumab arm and n=51 patients with a response in the chemotherapy arm
ᵖ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

Figure 23: Kaplan-Meier Curve for PFS in KEYNOTE-177



14.10 Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma for Tumors Expressing PD-L1 (CPS ≥1)

The efficacy of intravenous pembrolizumab in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811 (NCT03615326), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS $\geq$1 or CPS <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms:

- Intravenous pembrolizumab 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Treatment with intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. The major outcome measures assessed were PFS by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS.

Additional outcome measures included ORR and DoR, based on BICR using RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 698 patients randomized, 594 (85%) had tumors that expressed PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. 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.

A statistically significant improvement in OS and PFS was demonstrated in patients randomized to intravenous pembrolizumab in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy; however, an exploratory analysis of OS in the PD-L1 CPS <1 population showed a HR of 1.10 (95% CI: 0.72, 1.68), indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1.

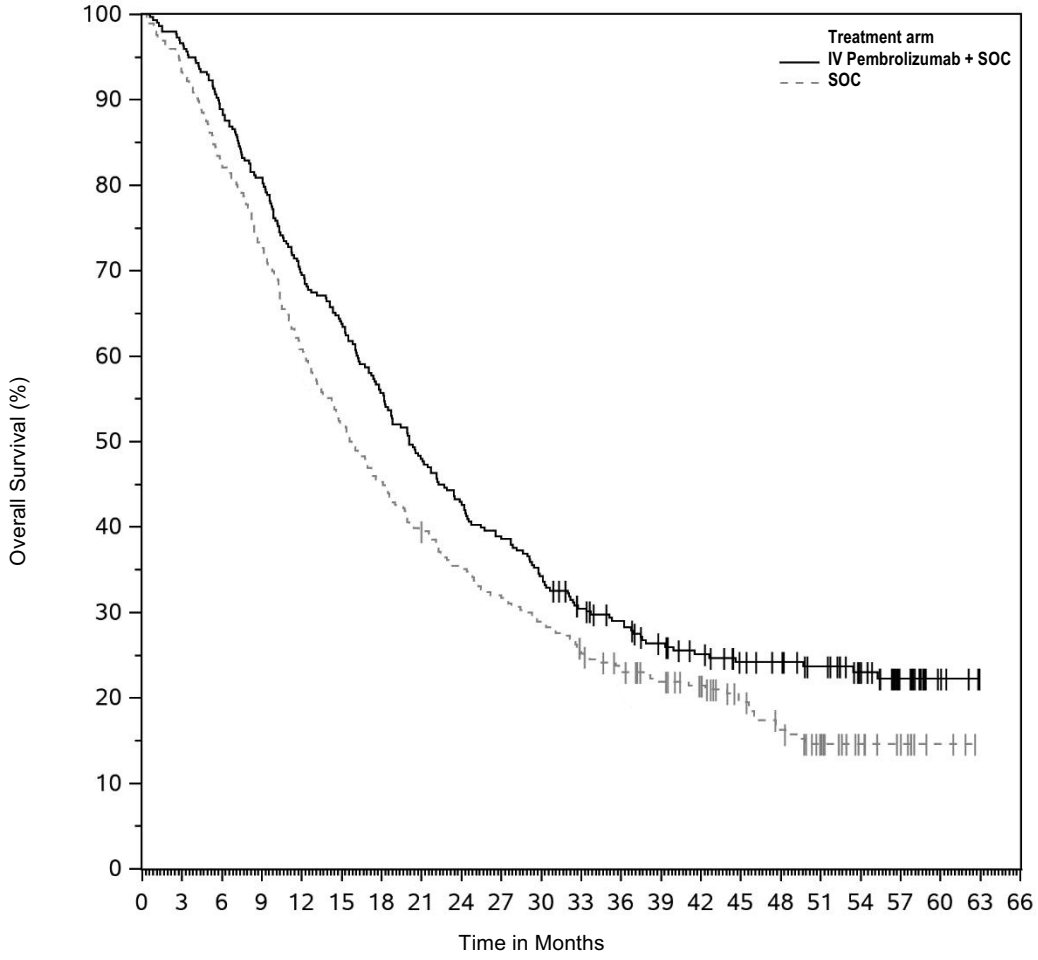
Efficacy results at the final analysis for the subgroup of patients whose tumors expressed PD-L1 with a CPS ≥1 are summarized in Table 87 and Figure 24.

Table 87: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥1

Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=298**	**Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=296**
OS		
Number (%) of patients with event	226 (76%)	244 (82%)
Median in months‡ (95% CI)	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
Hazard ratio* (95% CI)	0.79 (0.66, 0.95)	
PFS		
Number (%) of patients with event	221 (74%)	226 (76%)
Median in months‡ (95% CI)	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)
Hazard ratio* (95% CI)	0.72 (0.60, 0.87)	
Objective Response Rate		
ORR† (95% CI)	73% (68, 78)	58% (53, 64)
Complete response rate	17%	10%
Partial response rate	56%	48%
Duration of Response	n=218	n=173
Median in months‡ (95% CI) Range in months	11.3 (9.9, 13.7) 1.1+, 60.8+	9.6 (7.1, 11.2) 1.4+, 60.5+

* Based on the unstratified Cox proportional hazard model
† Response: Best objective response as confirmed complete response or partial response
‡ Based on Kaplan-Meier estimation
\+ Denotes ongoing response

Figure 24: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



Number at Risk

IV Pembrolizumab + SOC	298	288	265	241	207	190	166	143	127	115	102	86	78	67	59	51	48	42	32	18	5	0	0
SOC	296	276	244	215	180	154	135	117	104	93	85	73	63	56	50	38	30	21	13	9	3	0	0

First-line Treatment of Locally Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma for Tumors Expressing PD-L1 (CPS ≥1)

The efficacy of intravenous pembrolizumab in combination with fluoropyrimidine- and platinum-containing chemotherapy was investigated in KEYNOTE-859 (NCT03675737), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or GEJ adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥1 or CPS <1), chemotherapy regimen (FP or CAPOX), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms:

- Intravenous pembrolizumab 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Platinum agents could be administered for 6 or more cycles following local guidelines. Treatment with intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. The major efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DoR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among 1,579 patients, 1,235 (78%) had tumors expressing PD-L1 CPS ≥ 1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. The population characteristics in patients with PD-L1 CPS ≥ 1 expressing tumors were: median age of 62 years (range: 24 to 86), 40% age 65 or older; 70% male and 30% female; 55% White, 33% Asian, 4.6% Multiple, 4.3% American Indian or Alaskan Native, 1.3% Black, and 0.2% Native Hawaiian or other Pacific Islander; 76% Not Hispanic or Latino and 21% Hispanic or Latino; 37% ECOG PS of 0 and 63% ECOG PS of 1. Ninety-six percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Five percent (n=66) had tumors that were MSI-H. Eighty-six percent of patients received CAPOX.

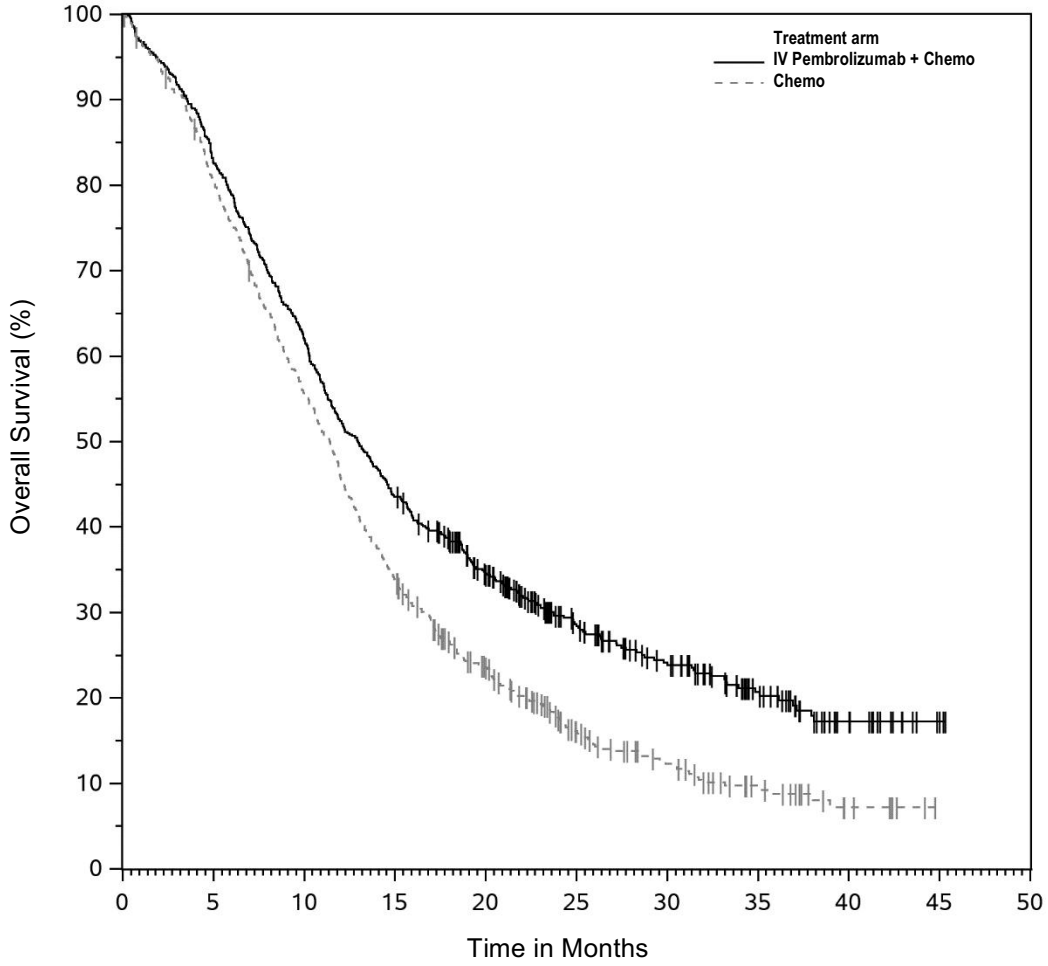
A statistically significant improvement in OS, PFS, and ORR was demonstrated in patients randomized to intravenous pembrolizumab in combination with chemotherapy compared with placebo in combination with chemotherapy at the time of a pre-specified interim analysis of OS; however, an exploratory analysis of OS in the PD-L1 CPS <1 population showed a HR of 0.92 (95% CI 0.73, 1.17) indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1. Efficacy results for patients whose tumors expressed PD-L1 CPS ≥1 and CPS ≥10 are summarized in Table 88 and Figures 25 and 26.

Table 88: Efficacy Results* for KEYNOTE-859

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks and FP or CAPOX n=618	Placebo and FP or CAPOX n=617	Intravenous Pembrolizumab 200 mg every 3 weeks and FP or CAPOX n=279	Placebo and FP or CAPOX n=272
	CPS ≥1		CPS ≥10	
OS				
Number (%) of patients with event	464 (75)	526 (85)	188 (67)	226 (83)
Median in months (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
Hazard ratio† (95% CI)	0.74 (0.65, 0.84)		0.65 (0.53, 0.79)	
p-Value (stratified log-rank)‡	<0.0001		<0.0001	
PFS				
Number (%) of patients with event	443 (72%)	483 (78%)	190 (68)	210 (77)
Median in months (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
Hazard ratio† (95% CI)	0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
p-Value (stratified log-rank)‡	<0.0001		<0.0001	
Objective Response Rate				
ORR§ (95% CI)	52% (48, 56)	43% (39, 47)	61% (55, 66)	43% (37, 49)
Complete response rate	10%	6%	13%	5%
Partial response rate	42%	37%	48%	38%
p-Value¶	0.0004		<0.0001	
Duration of Response	n=322	n=263	n=169	n=117
Median in months# (95% CI)	8.3 (7.0, 10.9)	5.6 (5.4, 6.9)	10.9 (8.0, 13.8)	5.8 (5.3, 7.0)
Range in months	1.2+, 41.5+	1.3+, 34.2+	1.2+, 41.5+	1.4+, 31.2+

* Based on a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ One-sided p-Value based on stratified Miettinen & Nurminen method
# Based on Kaplan-Meier estimates
\+ Denotes ongoing response

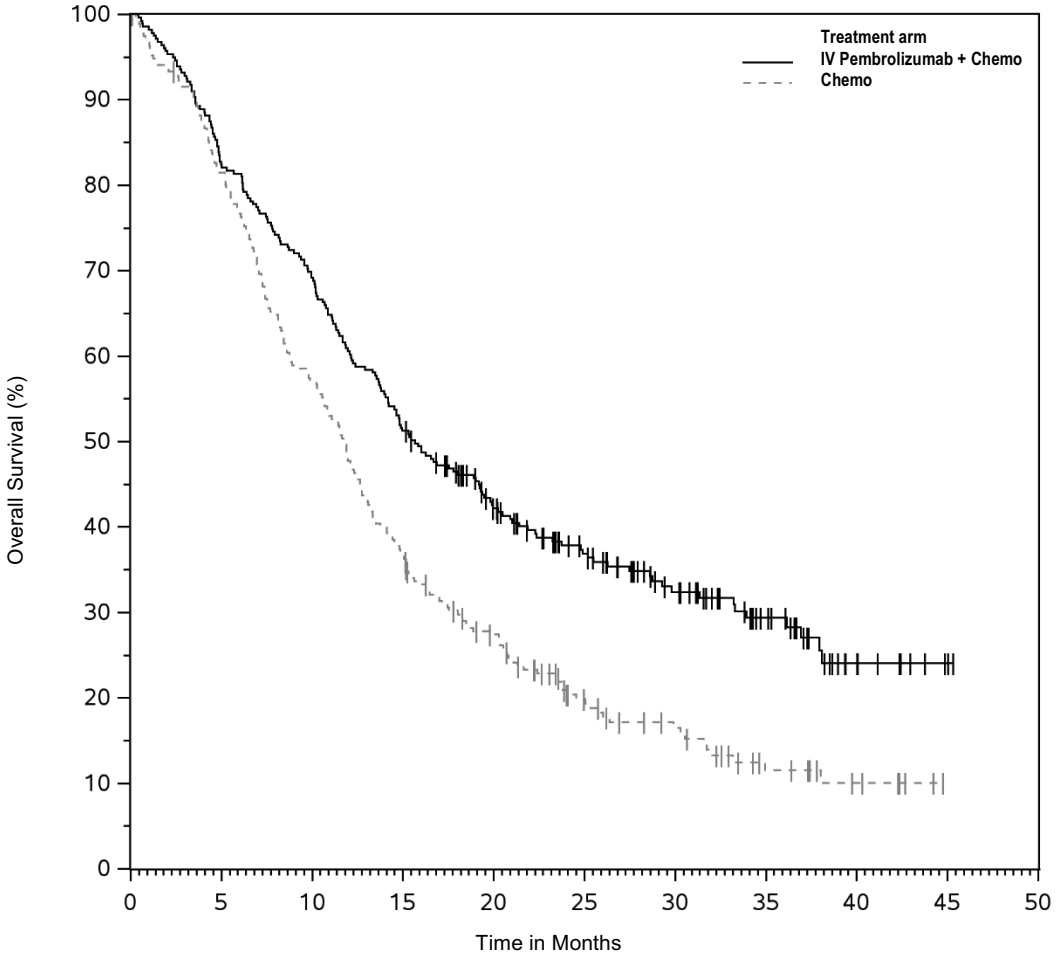
Figure 25: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS ≥1)



Number at Risk

IV Pembrolizumab + Chemo	618	511	383	269	192	121	81	46	17	3	0
Chemo	617	493	339	206	126	66	41	20	7	0	0

Figure 26: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS ≥10)



Number at Risk											
IV Pembrolizumab + Chemo	279	230	193	143	104	76	52	30	10	2	0
Chemo	272	220	154	99	67	37	26	12	6	0	0

An exploratory analysis of OS in the 74 patients with MSI-H tumors irrespective of PD-L1 status showed a HR of 0.34 (95% CI: 0.18, 0.66).

14.11 Esophageal Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal/Gastroesophageal Junction Cancer for Tumors Expressing PD-L1 (CPS ≥1)

KEYNOTE-590

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation. PD-L1 status was centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx assay. Patients with active autoimmune disease, a medical condition that required immunosuppression, or who received prior systemic therapy in the locally advanced or metastatic setting were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- Intravenous pembrolizumab 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

Treatment with intravenous pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. Patients could be treated with intravenous pembrolizumab for up to 24 months in the absence of disease progression. The major efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). The study pre-specified analyses of OS and PFS based on squamous cell histology, CPS ≥10, and in all patients. Additional efficacy outcome measures were ORR and DoR, according to modified RECIST v1.1, as assessed by the investigator. Additional analyses of efficacy outcome measures were also conducted based on PD-L1 CPS ≥1.

Among 749 patients, 647 (86%) had tumors expressing PD-L1 CPS ≥ 1. The study population characteristics in patients with PD-L1 CPS ≥ 1 expressing tumors were: median age of 63 years (range: 27 to 89), 41% age 65 or older; 83% male; 36% White, 54% Asian, and 1% Black; 40% had an ECOG PS of 0 and 59% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-four percent had a tumor histology of squamous cell carcinoma, and 26% had adenocarcinoma.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to intravenous pembrolizumab in combination with chemotherapy compared to chemotherapy; however, an exploratory analysis of OS in the PD-L1 CPS <1 population showed an HR of 0.96 (0.59, 1.55), indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1.

Table 89 and Figures 27 and 28 summarize the efficacy results for KEYNOTE-590 in patients whose tumors expressed PD-L1 CPS ≥1 and CPS ≥10.

Table 89: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Esophageal Cancer in KEYNOTE-590

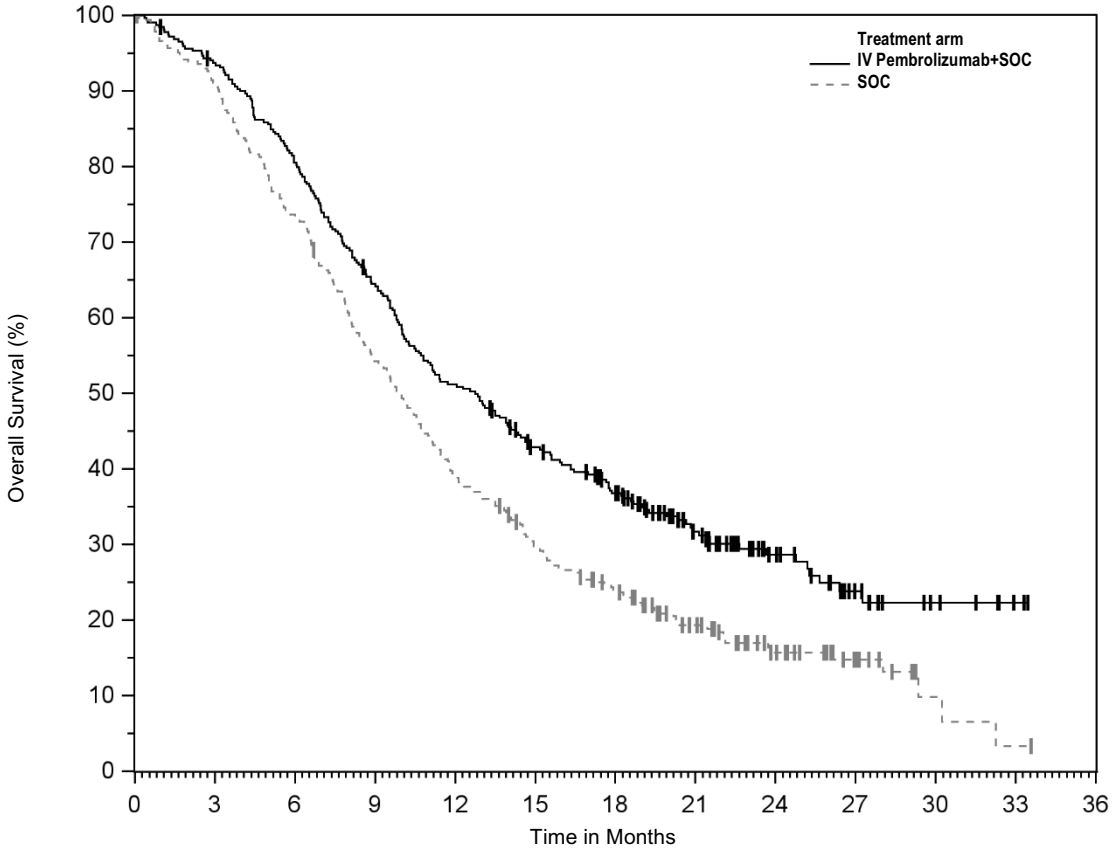
Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks Cisplatin FU n=320	Placebo Cisplatin FU n=327	Intravenous Pembrolizumab 200 mg every 3 weeks Cisplatin FU n=186	Placebo Cisplatin FU n=197
	CPS ≥1		CPS ≥10	
OS				
Number (%) of events	222 (69)	271 (83)	124 (67)	165 (84)
Median in months (95% CI)	12.7 (10.5, 14.4)	9.8 (8.8, 10.8)	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)
Hazard ratio* (95% CI)	0.71 (0.59, 0.84)		0.62 (0.49, 0.78)	
p-Value†			<0.0001	
PFS				
Number of events (%)	252 (79)	291 (89)	140 (75)	174 (88)
Median in months (95% CI)	6.3 (6.2, 7.1)	5.7 (4.6, 6.0)	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)
Hazard ratio* (95% CI)	0.62 (0.52, 0.73)		0.51 (0.41, 0.65)	
p-Value†			<0.0001	
Objective Response Rate				
ORR, %‡ (95% CI)	45 (40, 51)	29 (24, 34)	51 (44, 59)	27 (21, 34)
Number (%) of complete responses	19 (6)	9 (2.8)	11 (6)	5 (2.5)
Number (%) of partial responses	126 (39)	85 (26)	84 (45)	48 (24)
Duration of Response				
Median in months (range)	8.6 (1.2+, 31.0+)	5.8 (1.5+, 25.0+)	10.4 (1.9+, 28.9+)	5.6 (1.5+, 25.0+)

* Based on the stratified Cox proportional hazard model

† Based on a stratified log-rank test; p-Value for CPS ≥1 not included (not pre-specified subgroup)

‡ Confirmed complete response or partial response

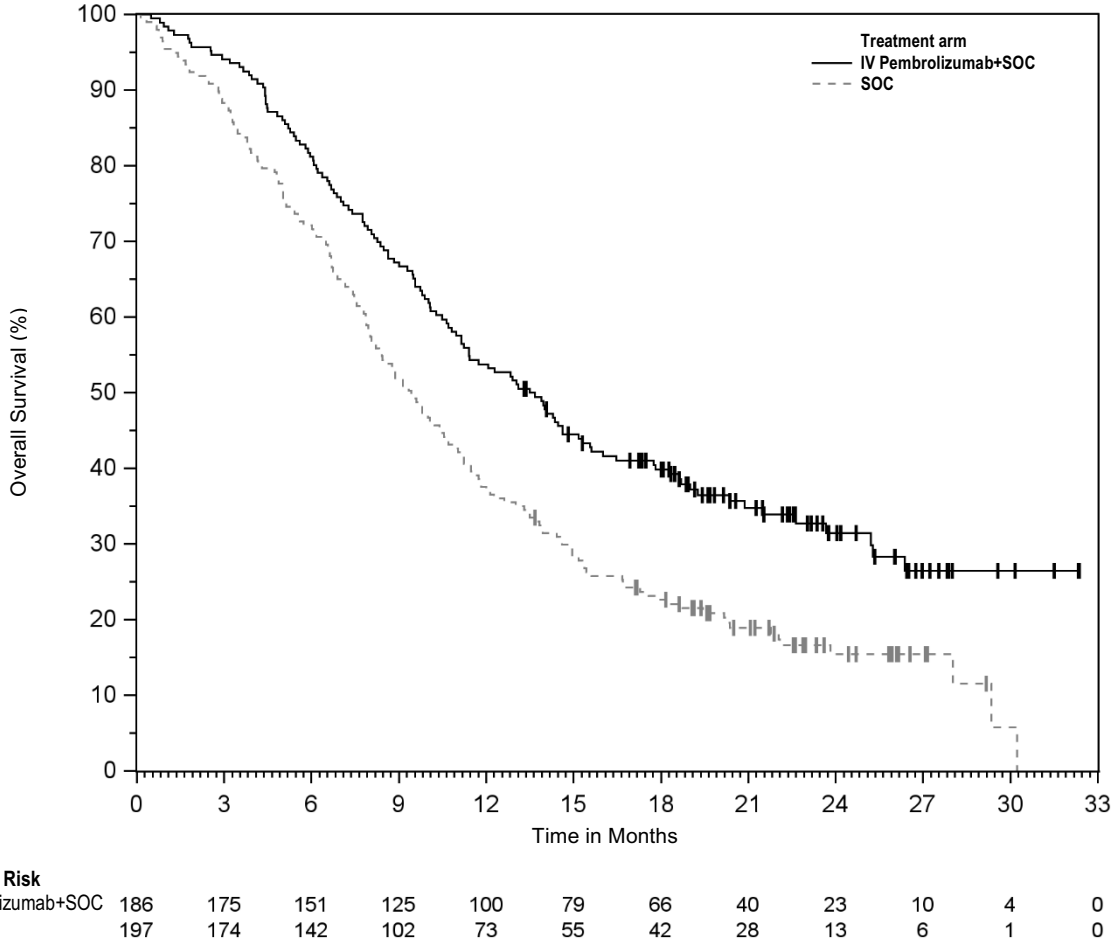
Figure 27: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590 (CPS ≥1)



Number at Risk

IV Pembrolizumab+SOC	320	298	256	204	162	130	106	61	34	16	7	2	0
SOC	327	297	240	176	126	94	72	47	25	13	3	1	0

Figure 28: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590 (CPS ≥10)



In a pre-specified formal test of OS in patients with PD-L1 CPS ≥10 (n=383), the median was 13.5 months (95% CI: 11.1, 15.6) for the intravenous pembrolizumab arm and 9.4 months (95% CI: 8.0, 10.7) for the placebo arm, with a HR of 0.62 (95% CI: 0.49, 0.78; p-Value < 0.0001). In an exploratory analysis, in patients with PD-L1 CPS <10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the intravenous pembrolizumab arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with a HR of 0.86 (95% CI: 0.68, 1.10).

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer for Tumors Expressing PD-L1 (CPS≥ 10)

KEYNOTE-181

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. Patients with a history of non-infectious pneumonitis that required steroids or

current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either intravenous pembrolizumab 200 mg every 3 weeks or investigator's choice of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (esophageal squamous cell carcinoma [ESCC] vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with intravenous pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to intravenous pembrolizumab were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with intravenous pembrolizumab without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measure was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. Additional efficacy outcome measures were PFS, ORR, and DoR, according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to intravenous pembrolizumab (n=314) or investigator's treatment of choice (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 patients were randomized to intravenous pembrolizumab and 82 patients to investigator's treatment of choice [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)]. The baseline characteristics of these 167 patients were: median age of 65 years (range: 33 to 80), 51% age 65 or older; 84% male; 32% White and 68% Asian; 38% had an ECOG PS of 0 and 62% had an ECOG PS of 1. Ninety percent had M1 disease and 10% had M0 disease. Prior to enrollment, 99% of patients had received platinum-based treatment and 84% had also received treatment with a fluoropyrimidine. Thirty-three percent of patients received prior treatment with a taxane.

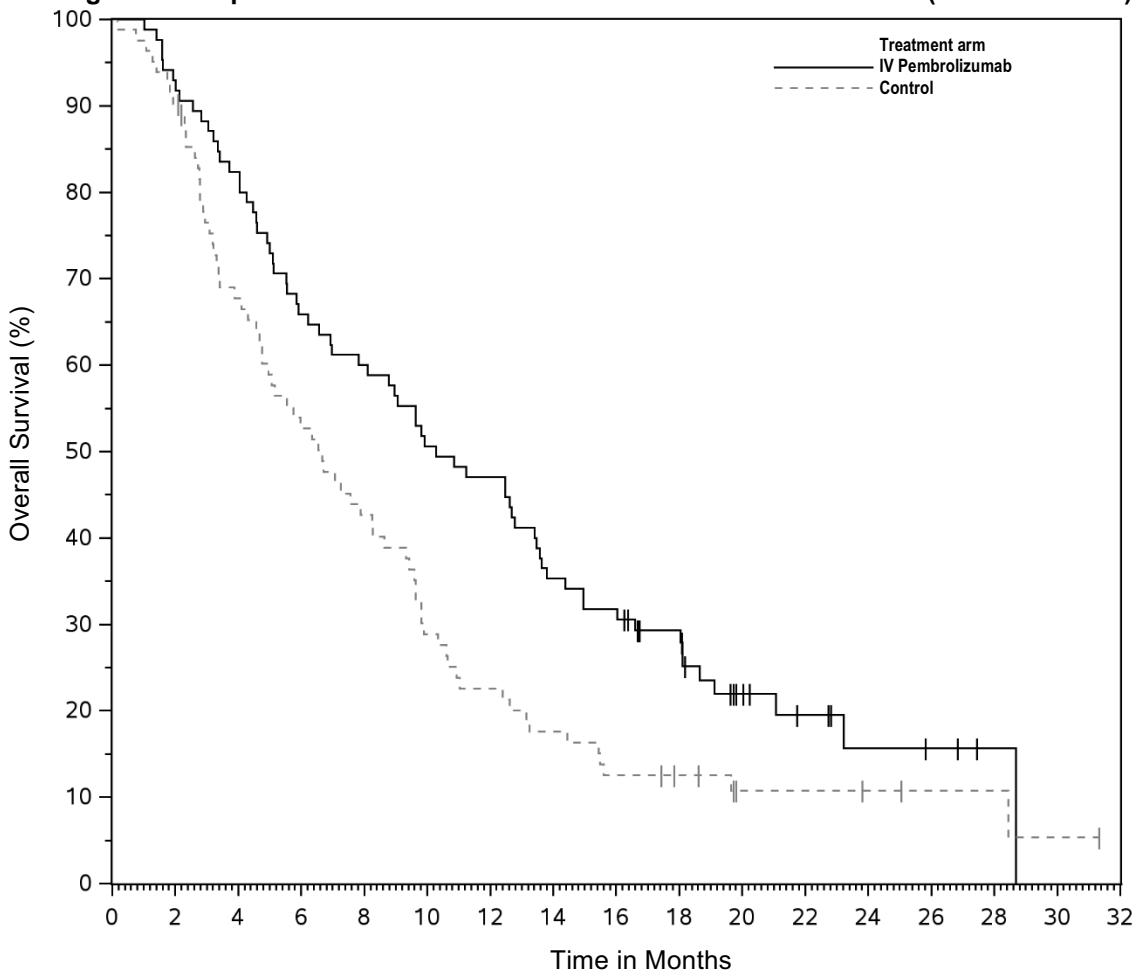
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to intravenous pembrolizumab as compared with chemotherapy. Table 90 and Figure 29 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 90: Efficacy Results in Patients with Recurrent or Metastatic ESCC (CPS ≥10) in KEYNOTE-181

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=85	Chemotherapy n=82
OS		
Number (%) of patients with event	68 (80%)	72 (88%)
Median in months (95% CI)	10.3 (7.0, 13.5)	6.7 (4.8, 8.6)
Hazard ratio* (95% CI)	0.64 (0.46, 0.90)	
PFS		
Number (%) of patients with event	76 (89%)	76 (93%)
Median in months (95% CI)	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
Hazard ratio* (95% CI)	0.66 (0.48, 0.92)	
Objective Response Rate		
ORR (95% CI)	22 (14, 33)	7 (3, 15)
Number (%) of complete responses	4 (5)	1 (1)
Number (%) of partial responses	15 (18)	5 (6)
Median duration of response in months (range)	9.3 (2.1+, 18.8+)	7.7 (4.3, 16.8+)

* Based on the Cox regression model stratified by geographic region (Asia vs. ex-Asia)

Figure 29: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS ≥10)



Number at Risk

IV Pembrolizumab	85	79	70	56	51	43	40	30	27	21	11	7	4	3	1	0	0
Control	82	74	54	42	34	23	18	14	10	8	4	4	3	2	2	1	0

KEYNOTE-180

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-180 (NCT02559687), a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. With the exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181.

The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The baseline characteristics of these 35 patients were: median age of 65 years (range: 47 to 81), 51% age 65 or older; 71% male; 26% White and 69% Asian; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. One hundred percent had M1 disease.

The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8, 37). Among the 7 responding patients, the DoR ranged from 4.2 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer.

14.12 Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The efficacy of intravenous pembrolizumab in combination with CRT (cisplatin and external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18 (NCT04221945), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1060 patients with cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 599 patients with FIGO 2014 Stage III-IVA disease (tumor involves the lower third of the vagina or the pelvic sidewall, or there is hydronephrosis/non-functioning kidney or spread to adjacent pelvic organs, all without spread to distant organs), and 459 patients with FIGO 2014 Stage IB2-IIB disease (clinical lesion >4 cm confined to the cervix, or clinical lesion of any size with extension beyond the uterus, but which has not extended to the pelvic wall or lower third of the vagina) with positive nodes. Two patients had FIGO 2014 Stage IVB disease. Randomization was stratified by planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. FIGO 2014 Stage III-IVA), and planned total radiotherapy dose (EBRT + brachytherapy dose of <70 Gy vs. ≥70 Gy as per equivalent dose [EQD2]).

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

- Intravenous pembrolizumab 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 intravenous pembrolizumab 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity.

Assessment of tumor status was performed every 12 weeks from completion of CRT for the first two years, followed by every 24 weeks in year 3, and then annually. The major efficacy outcome measures were PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or histopathologic confirmation, and OS.

Among the 599 patients with FIGO 2014 Stage III-IVA disease, the baseline characteristics were: median age of 52 years (range: 22 to 87), 17% age 65 or older; 36% White, 34% Asian, 2% Black; 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) and 29% had neither positive pelvic nor para-aortic lymph node(s); 83% had squamous cell carcinoma and 17% had non-squamous histology. Regarding radiation, 86% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 7 to 114).

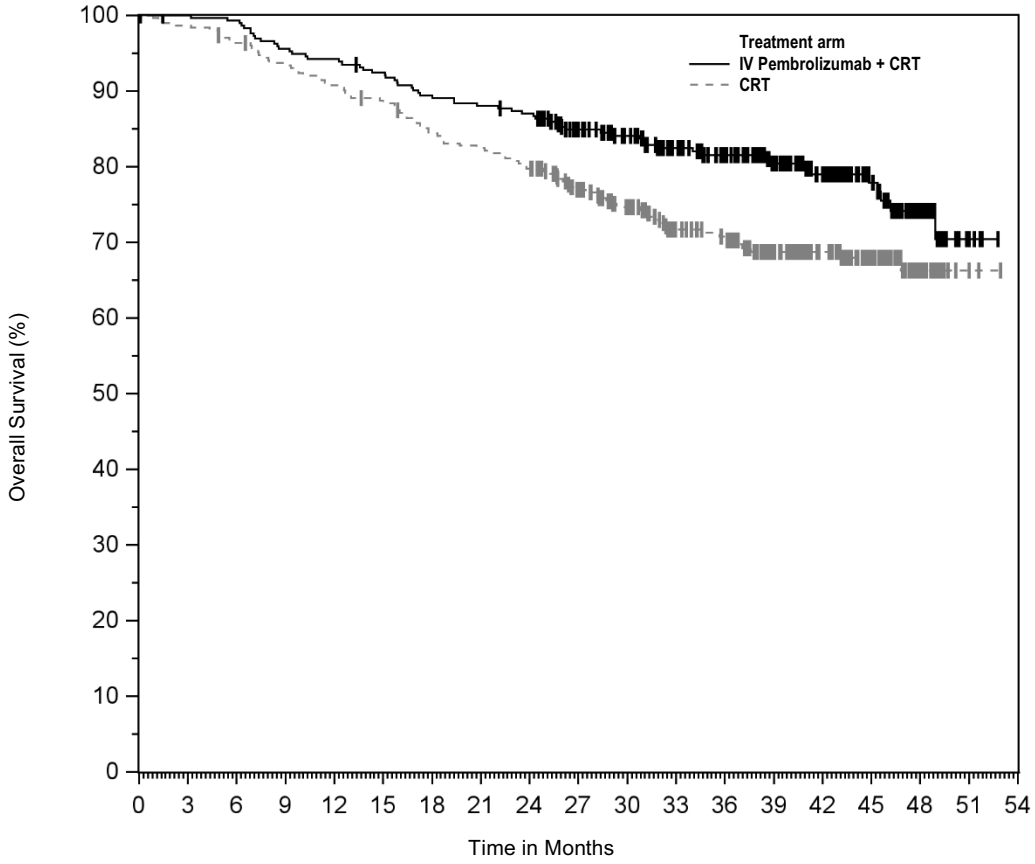
The trial demonstrated statistically significant improvements in PFS and OS in the ITT population. Exploratory analyses of PFS and OS by the stratification factor of FIGO 2014 stage showed that the improvement in the ITT population was primarily attributed to the results seen in the patients with FIGO 2014 Stage III-IVA disease. Table 91 and Figures 30 and 31 summarize the results in exploratory subgroup analyses of 599 patients with FIGO 2014 Stage III-IVA disease.

Table 91: Efficacy Results in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=295	Placebo with CRT n=304
OS*		
Number of patients with event (%)	61 (21)	90 (30)
Hazard ratio† (95% CI)	0.65 (0.47, 0.90)	
PFS by Investigator‡		
Number of patients with event (%)	61 (21)	94 (31)
Median in months (95% CI)	NR (NR, NR)	NR (18.8, NR)
12-month PFS rate (95% CI)	81% (75, 85)	70% (64, 76)
Hazard ratio† (95% CI)	0.59 (0.43, 0.81)	

CRT = Chemoradiotherapy
NR = not reached
*Results at the time of pre-specified final analysis for OS
† Based on the unstratified Cox proportional hazard model
‡ Results at the time of first pre-specified interim analysis for PFS

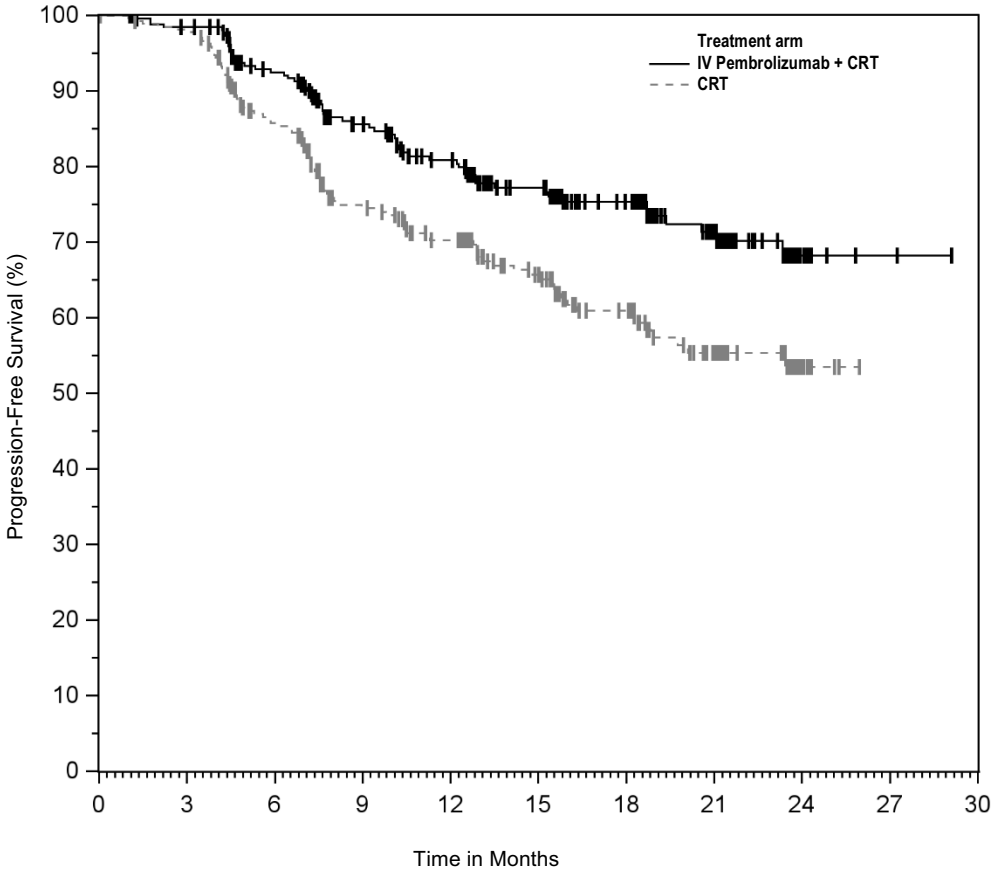
Figure 30: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)



Number at Risk

IV Pembrolizumab + CRT	295	293	291	280	276	270	261	257	253	226	209	189	167	137	105	70	30	4	0
CRT	304	300	292	283	274	266	253	247	239	210	186	160	149	118	91	59	23	2	0

Figure 31: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)



Number at Risk											
IV Pembrolizumab + CRT	295	255	224	187	163	129	96	62	11	2	0
CRT	304	261	209	163	142	109	78	46	8	0	0

Persistent, Recurrent, or Metastatic Cervical Cancer for Tumors Expressing PD-L1 (CPS ≥1)

The efficacy of intravenous pembrolizumab in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826 (NCT03635567), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumor PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10). Patients were randomized (1:1) to one of the two treatment groups:

- Treatment Group 1: Intravenous pembrolizumab 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomization:

1. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2
2. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. Treatment with intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of intravenous pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 9 weeks for the first year, followed by every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by investigator.

Of the 617 enrolled patients, 548 patients (89%) had tumors expressing PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. Among these 548 enrolled patients with tumors expressing PD-L1, 273 patients were randomized to intravenous pembrolizumab in combination with chemotherapy with or without bevacizumab, and 275 patients were randomized to placebo in combination with chemotherapy with or without bevacizumab. Sixty-three percent of the 548 patients received bevacizumab as part of study treatment. The baseline characteristics of the 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, 6% American Indian or Alaska Native, and 1% Black; 37% Hispanic or Latino; 56% ECOG performance status 0 and 43% ECOG performance status 1. Seventy-five percent had squamous cell carcinoma, 21% adenocarcinoma, and 5% adenosquamous histology, and 32% of patients had metastatic disease at diagnosis. At study entry, 21% of patients had metastatic disease only and 79% had persistent or recurrent disease with or without distant metastases, of whom 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

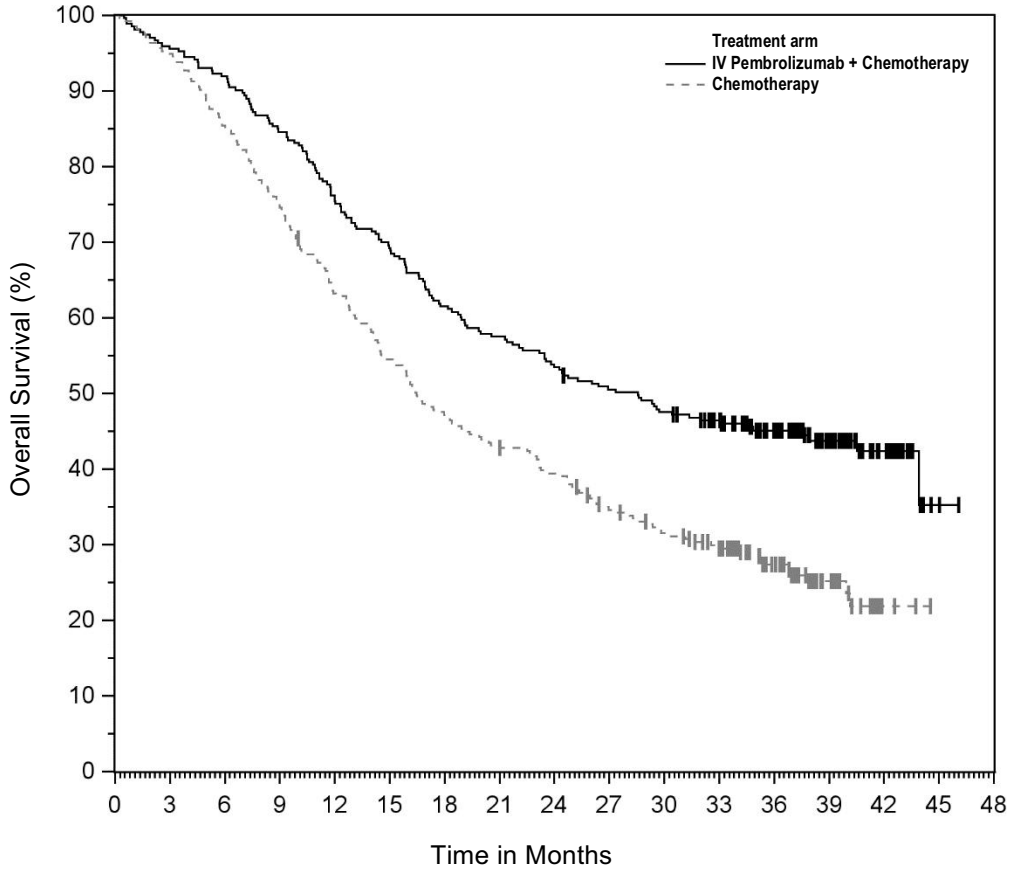
A statistically significant improvement in OS and PFS was demonstrated in patients randomized to receive intravenous pembrolizumab compared with patients randomized to receive placebo. An updated OS analysis was conducted at the time of final analysis when 354 deaths in the CPS ≥1 population were observed. Table 92 and Figure 32 summarize the key efficacy measures for KEYNOTE-826 for patients with tumors expressing PD-L1 (CPS ≥1).

Table 92: Efficacy Results in Patients with Persistent, Recurrent, or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-826

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=273	Placebo and chemotherapy* with or without bevacizumab n=275
OS		
Number of patients with event (%)	118 (43.2)	154 (56.0)
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
Hazard ratio† (95% CI)	0.64 (0.50, 0.81)	
p-Value‡	0.0001	
Updated OS		
Number of patients with event (%)	153 (56.0%)	201 (73.1%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
PFS		
Number of patients with event (%)	157 (57.5)	198 (72.0)
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio† (95% CI)	0.62 (0.50, 0.77)	
p-Value§	< 0.0001	
Objective Response Rate		
ORR¶ (95% CI)	68% (62, 74)	50% (44, 56)
Complete response rate	23%	13%
Partial response rate	45%	37%
Duration of Response		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0055 for this interim analysis (with 72% of the planned number of events for final analysis)
§ p-Value (one-sided) is compared with the allocated alpha of 0.0014 for this interim analysis (with 82% of the planned number of events for final analysis)
¶ Response: Best objective response as confirmed complete response or partial response
\+ Denotes ongoing response
NR = not reached

Figure 32: Kaplan-Meier Curve for Overall Survival in KEYNOTE-826 (CPS ≥1)*,†



Number at Risk																	
IV Pembrolizumab + Chemotherapy	273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
Chemotherapy	275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

*Treatment arms include intravenous pembrolizumab plus chemotherapy, with or without bevacizumab, versus placebo plus chemotherapy, with or without bevacizumab.
†Based on the protocol-specified final OS analysis

Previously Treated Recurrent or Metastatic Cervical Cancer for Tumors Expressing PD-L1 (CPS≥ 1)

The efficacy of intravenous pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received intravenous pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

Among the 98 patients in Cohort E, 77 (79%) had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy in the metastatic setting. PD-L1 status was determined using the IHC 22C3 pharmDx assay. The baseline characteristics of these 77 patients were: median age of 45 years (range: 27 to 75); 81% White, 14% Asian, and 3% Black; 32% ECOG PS of 0 and 68% ECOG PS of 1; 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology;

95% had M1 disease and 5% had recurrent disease; and 35% had one and 65% had two or more prior lines of therapy in the recurrent or metastatic setting.

No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 93 for patients with PD-L1 expression (CPS ≥1).

Table 93: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=77*
Objective Response Rate	
ORR (95% CI)	14.3% (7.4, 24.1)
Complete response rate	2.6%
Partial response rate	11.7%
Duration of Response	
Median in months (range)	NR (4.1, 18.6+)†
% with duration ≥6 months	91%

* Median follow-up time of 11.7 months (range: 0.6 to 22.7 months)
† Based on patients (n=11) with a response by independent review
\+ Denotes ongoing response
NR = not reached

14.13 Hepatocellular Carcinoma

Previously Treated HCC

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-394 (NCT03062358), a multicenter, randomized, placebo-controlled, double-blind trial conducted in Asia in patients with Barcelona Clinic Liver Cancer (BCLC) Stage B or C HCC, who were previously treated with sorafenib or oxaliplatin-based chemotherapy and who were not amenable to or were refractory to local-regional therapy. Patients were also required to have Child-Pugh A liver function.

Patients with hepatitis B had treated controlled disease (HBV viral load <2000 IU/mL or $<10^4$ copies/mL). Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Patients with hepatic encephalopathy, main branch portal venous invasion, clinically apparent ascites, or esophageal or gastric variceal bleeding within the last 6 months were also ineligible.

Randomization was stratified by prior treatment: sorafenib vs. oxaliplatin-based chemotherapy, macrovascular invasion, and etiology (active HBV vs. others (active HCV, non-infected)). Patients were randomized (2:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or placebo.

Treatment with intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks. The main efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study enrolled 453 patients, and 360 (79%) had active hepatitis B. The population characteristics in patients with active hepatitis B were: median age of 52 years (range: 23 to 82), 16% age 65 or older; 86% male; 100% Asian; 42% ECOG PS of 0 and 58% ECOG PS of 1; 90% received prior sorafenib and 10% received prior oxaliplatin-based chemotherapy. Patient characteristics also included extrahepatic disease (77%), macrovascular invasion (10%), BCLC stage C (93%) and B (7%), and baseline AFP ≥200 ng/mL (57%).

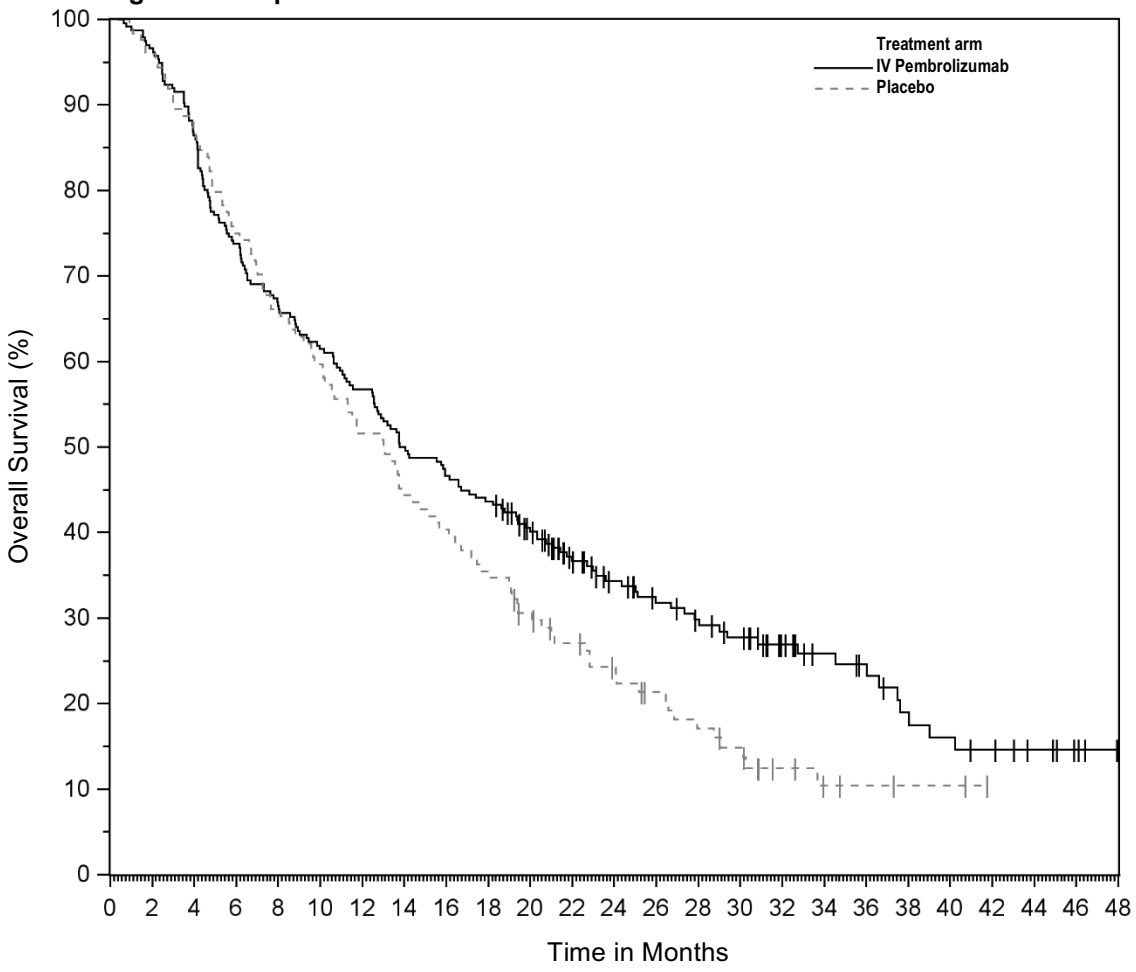
KEYNOTE-394 demonstrated improved OS in patients with HCC secondary to hepatitis B randomized to intravenous pembrolizumab compared with placebo. Efficacy results are summarized in Table 94 and Figure 33.

Table 94: Efficacy Results in Patients with Hepatocellular Carcinoma in KEYNOTE-394

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=236	Placebo n=124
OS*		
Number (%) of patients with events	172 (73)	105 (85)
Median in months (95% CI)	13.9 (12.5, 17.9)	13.0 (10.1, 15.6)
Hazard ratio† (95% CI)	0.78 (0.61, 0.99)	
PFS‡		
Number (%) of patients with events	189 (80)	108 (87)
Median in months (95% CI)	2 (1.4, 2.7)	2.3 (1.4, 2.8)
Hazard ratio† (95% CI)	0.78 (0.61, 1.00)	
Objective Response Rate‡		
ORR§ (95% CI)	11% (7, 16)	1.6% (0.2, 5.7)
Number (%) of complete responses	2 (0.9%)	1 (0.8%)
Number (%) of partial responses	24 (10%)	1 (0.8%)
Duration of Response*	n=28	n=2
Median in months¶ (range)	23.9 (2.6+, 44.4+)	5.6 (3.0+, 5.6)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ Results at pre-specified interim OS analysis
§ Confirmed complete response or partial response
¶ Based on Kaplan-Meier estimate
\+ Denotes ongoing response

Figure 33: Kaplan-Meier Curve for Overall Survival in KEYNOTE-394



14.14 Biliary Tract Cancer

The efficacy of intravenous pembrolizumab in combination with gemcitabine and cisplatin chemotherapy was investigated in KEYNOTE-966 (NCT04003636), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by region (Asia vs. non-Asia), locally advanced versus metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomized (1:1) to intravenous pembrolizumab 200 mg on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks, or placebo on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks. Study medications were administered via intravenous infusion. Treatment continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months. For gemcitabine, treatment could be continued beyond 8 cycles while for cisplatin, treatment could be administered for a maximum of 8 cycles.

Administration of intravenous pembrolizumab with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving

clinical benefit. Assessment of tumor status was performed at baseline and then every 6 weeks through 54 weeks, followed by every 12 weeks thereafter.

Study population characteristics were median age of 64 years (range: 23 to 85), 47% age 65 or older; 52% male; 49% White, 46% Asian, 1.3% Black or African American; 10% Hispanic or Latino; 46% ECOG PS of 0 and 54% ECOG PS of 1; 31% of patients had a history of hepatitis B infection, and 3% had a history of hepatitis C infection.

The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

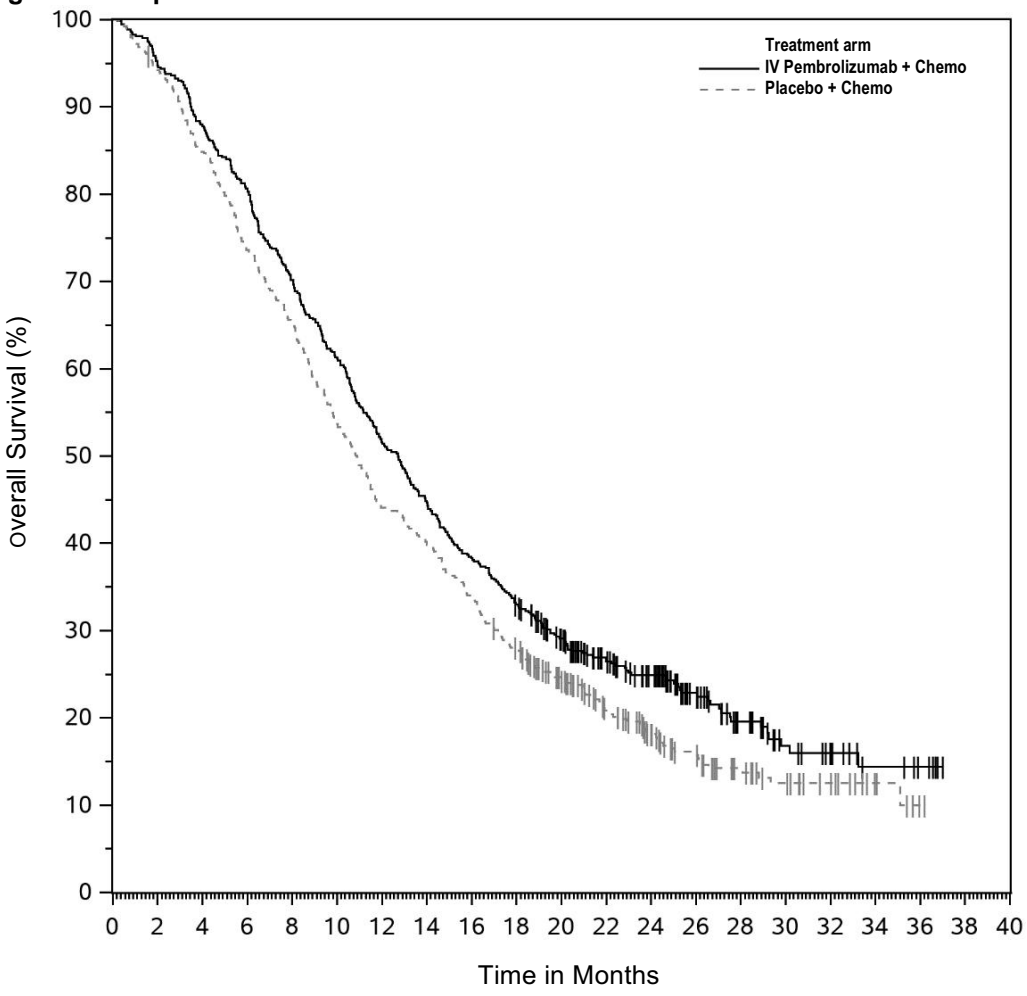
Table 95 and Figure 34 summarize the efficacy results for KEYNOTE-966.

Table 95: Efficacy Results in KEYNOTE-966

Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks with gemcitabine/cisplatin n=533**	**Placebo with gemcitabine/cisplatin n=536**
OS*		
Number of patients with event (%)	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio† (95% CI)	0.83 (0.72, 0.95)	
p-Value‡	0.0034	
PFS§		
Number (%) of patients with event	361 (68%)	391 (73%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (5.1, 6.6)
Hazard ratio† (95% CI)	0.86 (0.75, 1.00)	
p-Value‡	NS	
Objective Response Rate§		
ORR¶ (95% CI)	29% (25, 33)	29% (25, 33)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (27%)	146 (27%)
p-Value #	NS	
Duration of Response*	n=156	n=152
Median in months Þ (95% CI)	8.3 (6.9, 10.2)	6.8 (5.7, 7.1)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on a stratified log-rank test
§ Results at pre-specified final analysis of PFS and ORR
¶ Confirmed complete response or partial response
# One-sided p-Value based on the stratified Miettinen and Nurminen analysis
Þ Based on Kaplan-Meier estimate
NS = not significant

Figure 34: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966



14.15 Merkel Cell Carcinoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-017 (NCT02267603) and KEYNOTE-913 (NCT03783078), two multicenter, non-randomized, open-label trials that enrolled 105 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received intravenous pembrolizumab 2 mg/kg (KEYNOTE-017) or 200 mg (KEYNOTE-913) every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months.

The major efficacy outcome measures were ORR and DoR as assessed by BICR per RECIST v1.1.

Among the 105 patients enrolled, the median age was 73 years (range: 38 to 91), 79% were age 65 or older; 62% were male; 80% were White, race in 19% was unknown or missing, and 1% were Asian; 53% had ECOG PS of 0, and 47% had ECOG PS of 1. Thirteen percent had stage IIIB disease and 84% had stage IV. Seventy-six percent of patients had prior surgery and 51% had prior radiation therapy.

Efficacy results are summarized in Table 96.

Table 96: Efficacy Results in KEYNOTE-017 and KEYNOTE-913

Endpoint	KEYNOTE-017 Intravenous Pembrolizumab 2 mg/kg every 3 weeks n=50	KEYNOTE-913 Intravenous Pembrolizumab 200 mg or 2 mg/kg every 3 weeks n=55
Objective Response Rate		
ORR (95% CI)	56% (41, 70)	49% (35, 63)
Complete responses, n (%)	12 (24%)	9 (16%)
Partial responses, n (%)	16 (32%)	18 (33%)
Duration of Response	**n=28**	**n=27**
Median DoR in months (range)	NR (5.9, 34.5+)	NR (4.8, 25.4+)
Patients with duration ≥6 months, n (%)	27 (96%)	25 (93%)
Patients with duration ≥12 months, n (%)	15 (54%)	19 (70%)

\+ Denotes ongoing response
NR = not reached

14.16 Renal Cell Carcinoma

First-line treatment with axitinib

KEYNOTE-426

The efficacy of intravenous pembrolizumab in combination with axitinib was investigated in KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease requiring systemic immunosuppression within the last 2 years were ineligible. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”).

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

- Intravenous pembrolizumab 200 mg intravenously every 3 weeks up to 24 months in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive cycles (6 weeks) could increase to 7 mg and then subsequently to 10 mg twice daily. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

Treatment with intravenous pembrolizumab and axitinib continued until RECIST v1.1-defined progression of disease or unacceptable toxicity. Administration of intravenous pembrolizumab and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter.

The study population characteristics were: median age of 62 years (range: 26 to 90), 38% age 65 or older; 73% male; 79% White and 16% Asian; 20% and 80% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; and patient distribution by IMDC risk categories was 31% favorable, 56% intermediate, and 13% poor.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the first pre-specified interim analysis in patients randomized to intravenous pembrolizumab in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. An updated OS analysis was

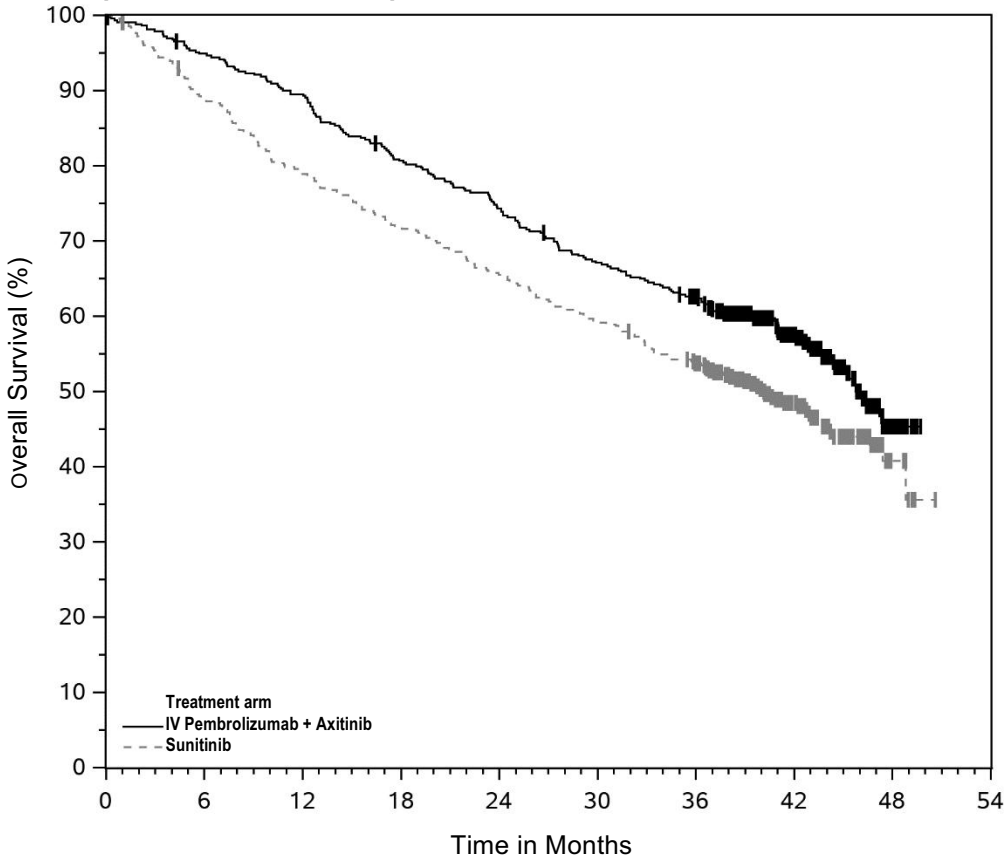
conducted when 418 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 97 and Figure 35 summarize the efficacy results for KEYNOTE-426.

Table 97: Efficacy Results in KEYNOTE-426

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks and Axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	<0.0001‡	
Updated OS		
Number of patients with event (%)	193 (45%)	225 (52%)
Median in months (95% CI)	45.7 (43.6, NR)	40.1 (34.3, 44.2)
Hazard ratio* (95% CI)	0.73 (0.60, 0.88)	
PFS		
Number of patients with event (%)	183 (42%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.0 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value†	0.0001§	
Objective Response Rate		
ORR¶ (95% CI)	59% (54, 64)	36% (31, 40)
Complete response rate	6%	2%
Partial response rate	53%	34%
p-Value#	<0.0001	

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).
§ p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region
NR = not reached

Figure 35: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-426



Number at Risk										
IV Pembrolizumab + Axitinib	432	407	384	345	318	286	259	141	16	0
Sunitinib	429	379	336	306	279	252	224	110	12	0

In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR of 1.17 (95% CI: 0.76, 1.80), 0.67 (95% CI: 0.52, 0.86), 0.64 (95% CI: 0.52, 0.80), and 0.51 (95% CI: 0.32, 0.81), respectively.

First-line treatment with lenvatinib

KEYNOTE-581

The efficacy of intravenous pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-581 (NCT02811861), a multicenter, open-label, randomized trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America versus Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable versus intermediate versus poor risk).

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

- Intravenous pembrolizumab 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.

- Lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

Treatment continued until unacceptable toxicity or disease progression. Administration of intravenous pembrolizumab with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. intravenous pembrolizumab was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 8 weeks.

The study population characteristics were: median age of 62 years (range: 29 to 88 years), 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by MSKCC risk categories was 27% favorable, 64% intermediate, and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

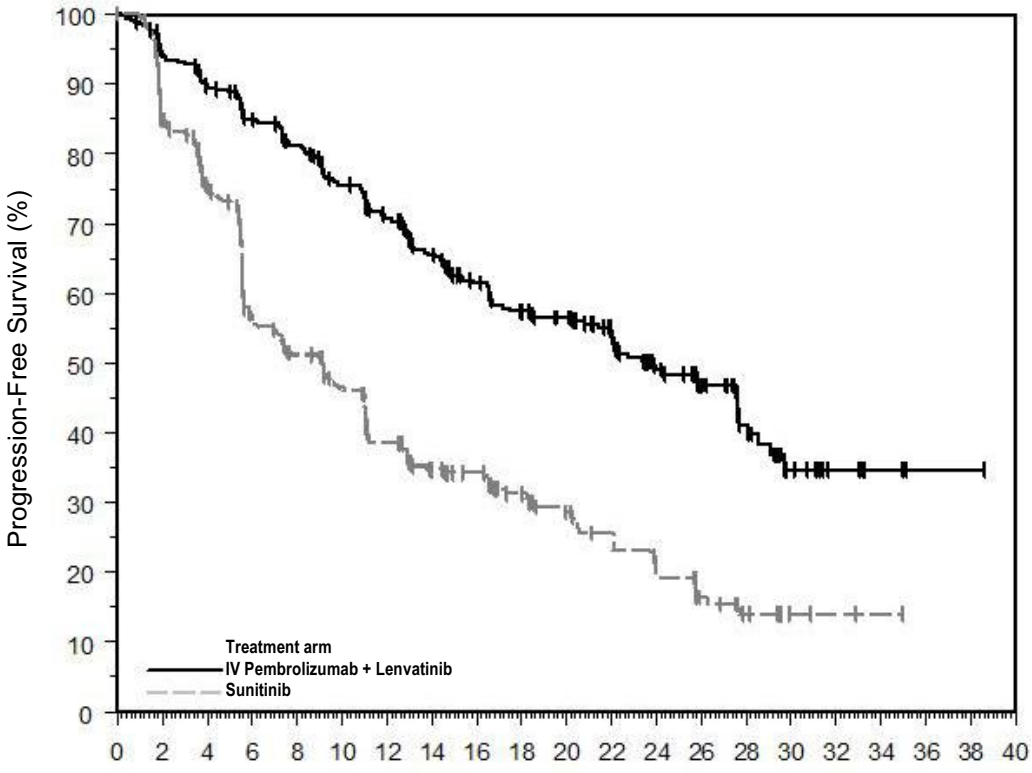
The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to RECIST v1.1, and OS. Additional efficacy outcome measures included confirmed ORR as assessed by IRC. intravenous pembrolizumab in combination with lenvatinib demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. An updated OS analysis was conducted when 304 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 98 and Figures 36 and 37 summarize the efficacy results for KEYNOTE-581.

Table 98: Efficacy Results in KEYNOTE-581

Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks and Lenvatinib n=355**	**Sunitinib n=357**
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45%)	205 (57%)
Progressive disease	145 (41%)	196 (55%)
Death	15 (4%)	9 (3%)
Median PFS in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value†	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (23%)	101 (28%)
Median OS in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.88)	
p-Value†	0.0049	
Updated OS		
Number of deaths, n (%)	149 (42%)	159 (45%)
Median OS in months (95% CI)	53.7 (48.7, NR)	54.3 (40.9, NR)
Hazard ratio* (95% CI)	0.79 (0.63, 0.99)	
Objective Response Rate (Confirmed)		
ORR, n (%)	252 (71%)	129 (36%)
(95% CI)	(66, 76)	(31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value‡	<0.0001	

Tumor assessments were based on RECIST 1.1; only confirmed responses are included for ORR.
Data cutoff date = 28 Aug 2020, Updated OS cutoff date = 31 July 2022
CI = confidence interval; NR= Not reached
* Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
† Two-sided p-Value based on stratified log-rank test.
‡ Two-sided p-Value based upon CMH test.

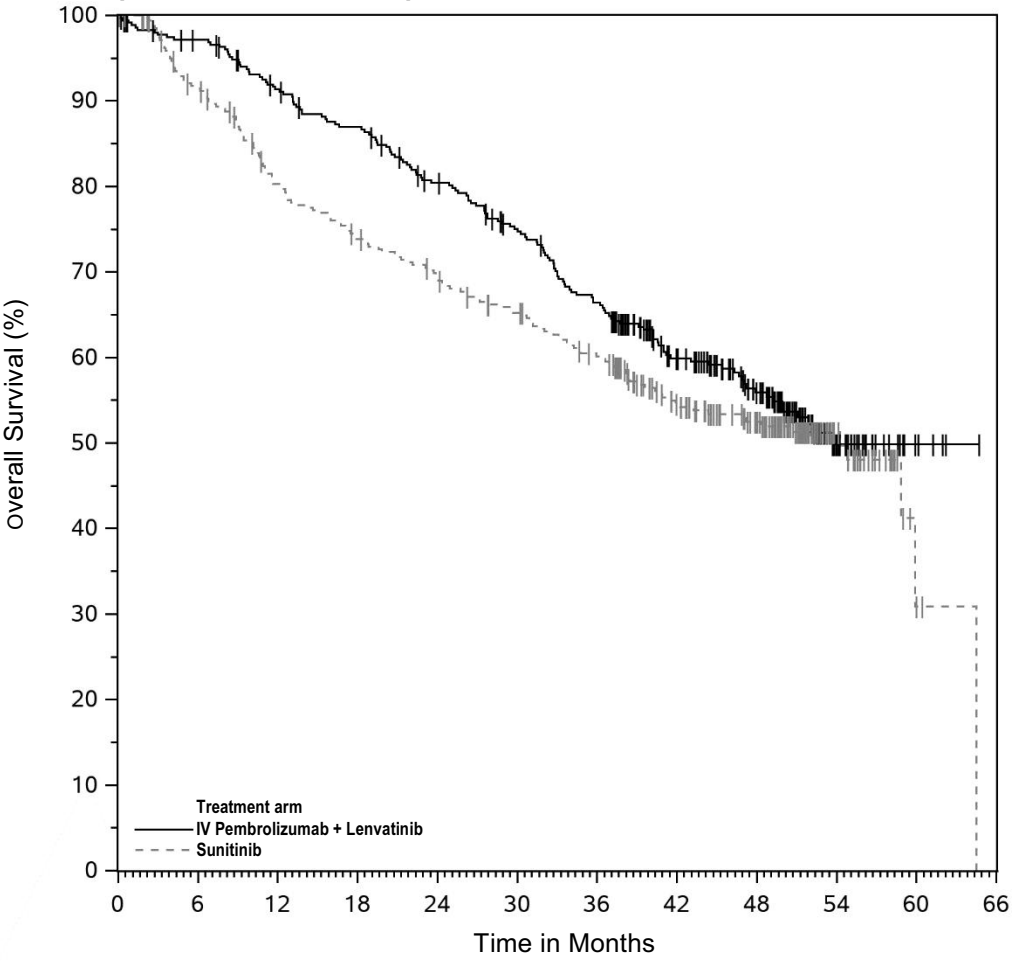
Figure 36: Kaplan-Meier Curve for PFS in KEYNOTE-581



Number at Risk

IV Pembrolizumab + Lenvatinib	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0	0	0

Figure 37: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-581



Number at Risk												
IV Pembrolizumab + Lenvatinib	355	338	313	296	269	245	216	158	117	34	5	0
Sunitinib	357	308	264	242	226	208	188	145	108	33	3	0

KEYNOTE-B61

The efficacy of intravenous pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-B61 (NCT04704219), a multicenter, single-arm trial that enrolled 160 patients with advanced or metastatic non-clear cell RCC in the first-line setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received intravenous pembrolizumab 400 mg every 6 weeks in combination with lenvatinib 20 mg orally once daily. Intravenous pembrolizumab was continued for a maximum of 24 months; however, lenvatinib could be continued beyond 24 months. Treatment continued until unacceptable toxicity or disease progression. Administration of intravenous pembrolizumab with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years); 71% male; 86% White, 8% Asian, and 3% Black; <1% Hispanic or Latino; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, <1% medullary, 13% unclassified, and 6% other; patient

distribution by IMDC risk categories was 35% favorable, 54% intermediate, and 10% poor. Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The major efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Additional efficacy outcome measures included DOR as assessed by BICR using RECIST 1.1. Efficacy results are summarized in Table 99.

Table 99: Efficacy Results in KEYNOTE-B61

Endpoint	Intravenous Pembrolizumab 400 mg every 6 weeks and Lenvatinib n=158
Objective Response Rate (Confirmed)	
ORR (95% CI)	51% (43, 59)
Complete response	8%
Partial response	42%
Duration of Response*	
Median in months (range)	19.5 (1.5+, 23.5+)

CI = confidence interval
* Based on Kaplan-Meier estimates
\+ Denotes ongoing response

Adjuvant Treatment of RCC (KEYNOTE-564)

The efficacy of intravenous pembrolizumab was investigated as adjuvant therapy for RCC in KEYNOTE-564 (NCT03142334), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate-high risk category included: pT2, Grade 4 only; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening. Patients were excluded from the trial if they had received prior systemic therapy for advanced RCC. Patients with active autoimmune disease or a medical condition that required immunosuppression were also ineligible. Patients were randomized to intravenous pembrolizumab 200 mg administered intravenously every 3 weeks or placebo for up to 1 year until disease recurrence or unacceptable toxicity. Randomization was stratified by metastasis status (M0, M1 NED); M0 group was further stratified by ECOG PS (0,1) and geographic region (US, non-US).

The study population characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; 75% White, 14% Asian, 9% Unknown, 1% Black or African American, 1% American Indian or Alaska Native, 1% Multiracial; 13% Hispanic or Latino, 78% Not Hispanic or Latino, 8% Unknown; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent of patients enrolled had N0 disease; 11% had sarcomatoid features; 86% were intermediate-high risk; 8% were high risk; and 6% were M1 NED. Ninety-two percent of patients had a radical nephrectomy, and 8% had a partial nephrectomy.

The major efficacy outcome measure was investigator-assessed disease-free survival (DFS), defined as time to recurrence, metastasis, or death. An additional outcome measure was OS. Statistically significant improvements in DFS and OS were demonstrated at pre-specified interim analyses in patients randomized to the intravenous pembrolizumab arm compared with placebo. Efficacy results are summarized in Table 100 and Figures 38 and 39.

Table 100: Efficacy Results in KEYNOTE-564

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks n=496	Placebo n=498
DFS		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.68 (0.53, 0.87)	
p-Value†	0.0010‡	
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)
OS		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.62 (0.44, 0.87)	
p-Value†	0.0024§	
48-month OS rate (95% CI)	91% (88, 93)	86% (83, 89)

* Based on the stratified Cox proportional hazard model

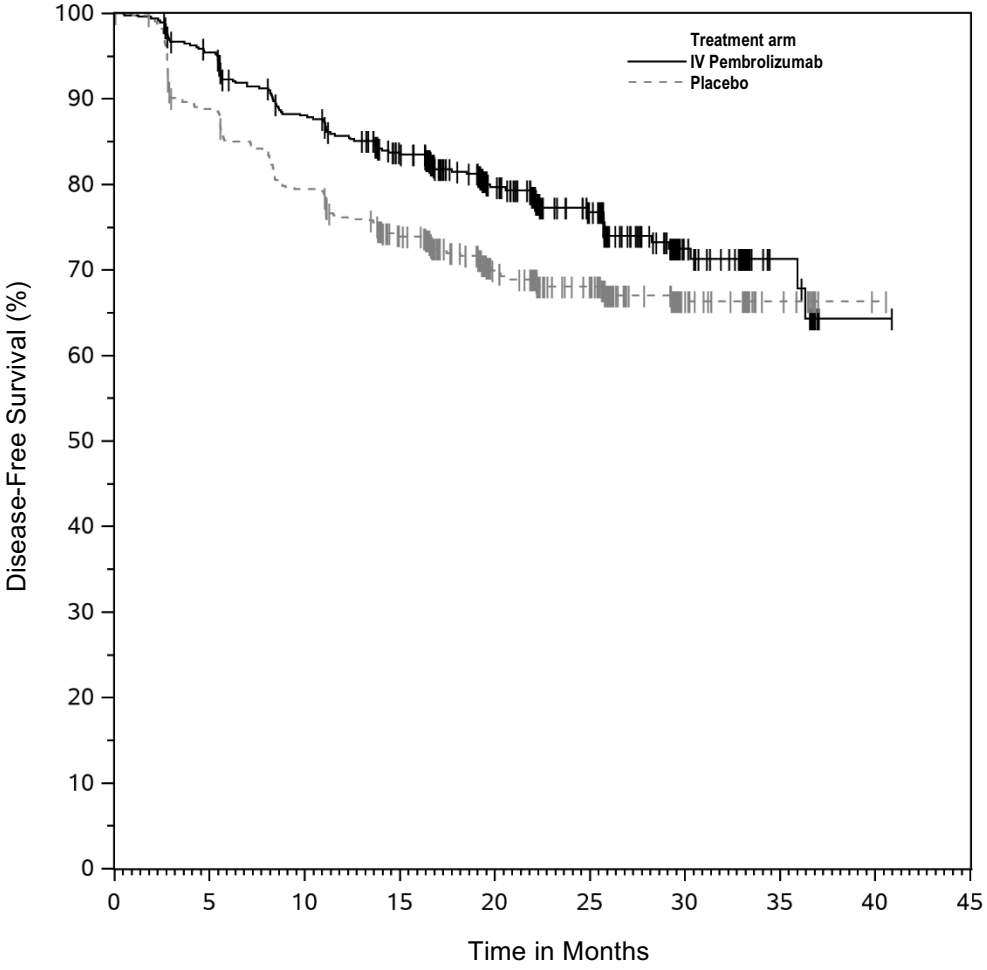
† Based on stratified log-rank test

‡ p-Value (one-sided) is compared with a boundary of 0.0114.

§ p-Value (one-sided) is compared with a boundary of 0.0072.

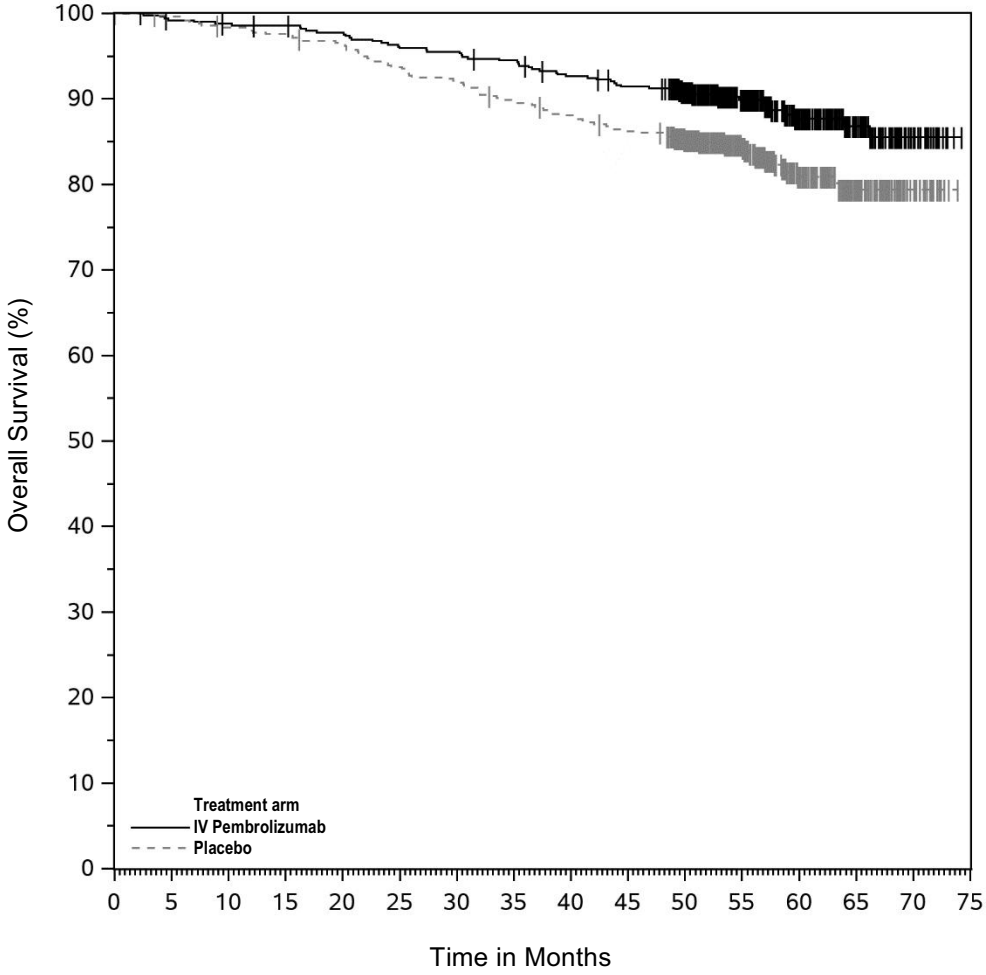
NR = not reached

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



Number at Risk										
IV Pembrolizumab	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

Figure 39: Kaplan-Meier Curve for Overall Survival in KEYNOTE-564



Number at Risk																
IV Pembrolizumab	496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo	498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

Adjuvant Treatment of ccRCC in Combination with Belzutifan (LITESPARK-022)

The efficacy of intravenous pembrolizumab in combination with belzutifan versus intravenous pembrolizumab in combination with placebo was investigated as adjuvant therapy for ccRCC in LITESPARK-022 (NCT05239728), a multicenter, randomized, double-blind trial in 1,841 patients with intermediate-high or high risk of recurrence of RCC, or M1 with no evidence of disease (NED). The intermediate-high risk category included: pT2, Grade 4 only; 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 were required to have undergone a partial or radical nephrectomy, and if indicated, metastasectomy within two years of nephrectomy, within ≥4 weeks prior to the time of screening. Patients were excluded from the trial if they had received prior systemic therapy for advanced RCC.

Patients were randomized (1:1) to receive intravenous pembrolizumab 400 mg every 6 weeks in combination with belzutifan 120 mg orally once daily (N=921) or intravenous pembrolizumab 400 mg every 6 weeks in combination with oral placebo (N=920) for up to 9 cycles (54 weeks) until disease recurrence or unacceptable toxicity. Randomization was stratified by risk of recurrence (intermediate-high, high risk, M1 NED) and tumor grade (1 or 2 versus 3 or 4).

The study population characteristics were: median age of 60 years (range: 20 to 91), 32% age 65 or older; 71% male; 63% White, 29% Asian, 3.6% Unknown, 0.7% Black or African American, 1.7% American Indian or Alaska Native, 1.8% Multiracial; 78% Not Hispanic or Latino, 15% Hispanic or Latino, 7% Unknown; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-six percent of patients enrolled had N0 disease or unknown nodal status; 10% had sarcomatoid features; 85% had intermediate-high risk; 6% had high risk; and 9% had M1 NED. Ninety percent of patients had a radical nephrectomy, and 10% had a partial nephrectomy.

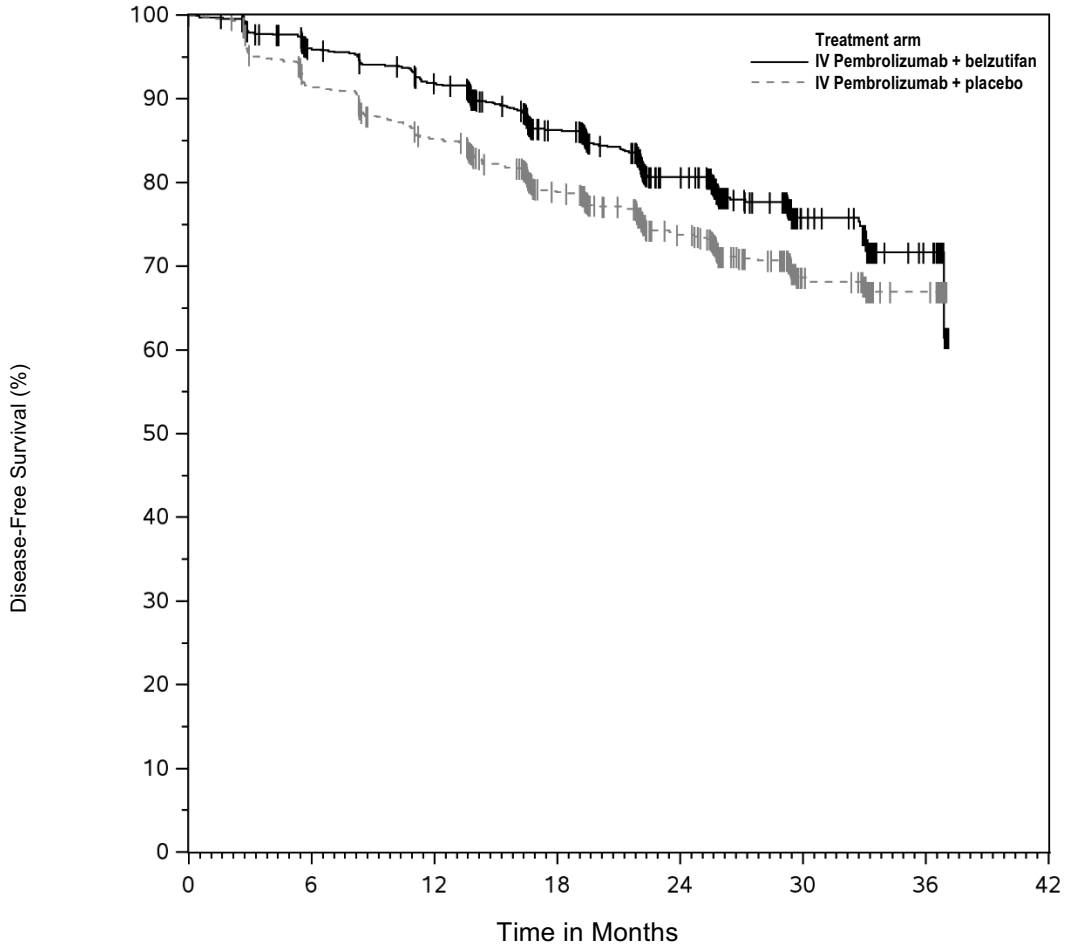
The major efficacy outcome measure was investigator-assessed disease-free survival (DFS), defined as time to recurrence, metastasis, or death. An additional outcome measure was overall survival (OS). A statistically significant improvement in DFS was demonstrated at pre-specified interim analysis in patients randomized to the intravenous pembrolizumab plus belzutifan arm compared with the intravenous pembrolizumab plus placebo arm. At the protocol pre-specified interim analysis, OS data were not mature with 29% of the required events for the final analysis. Efficacy results are summarized in Table 101 and Figure 40.

Table 101: Efficacy Results in LITESPARK-022

Efficacy Outcome Measure	Intravenous Pembrolizumab plus Belzutifan n=921	Intravenous Pembrolizumab plus Placebo n=920
DFS		
Number (%) of patients with event	186 (20%)	246 (27%)
Median in months* (95% CI)	NR (36.9, NR)	NR (NR, NR)
Hazard ratio† (95% CI)	0.72 (0.59, 0.87)	
p-Value	0.0003‡	
24-month DFS rate* (95% CI)	81% (78, 83)	74% (71, 77)

* Based on Kaplan-Meier estimates
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
CI = confidence interval; NR = not reached

Figure 40: Kaplan-Meier Curve for Disease-Free Survival in LITESPARK-022



Number at Risk

IV Pembrolizumab + belzutifan	921	850	805	669	451	153	35	0
IV Pembrolizumab + placebo	920	823	759	619	417	140	38	0

14.17 Endometrial Carcinoma

In Combination with Paclitaxel and Carboplatin for the Treatment of Primary Advanced or Recurrent Endometrial Carcinoma

The efficacy of intravenous pembrolizumab in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868/NRG-GY018 (NCT03914612), a multicenter, randomized, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma. The study design included two separate cohorts based on MMR status; 222 (27%) patients were in dMMR cohort, 588 (73%) patients were in pMMR cohort. The trial enrolled measurable Stage III, measurable Stage IVA, Stage IVB or recurrent endometrial cancer (with or without measurable disease). Patients who had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting were eligible. Patients who had received prior adjuvant chemotherapy were only eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy.

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

- Intravenous pembrolizumab 200 mg every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by intravenous pembrolizumab 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 intravenous pembrolizumab or placebo for up to 10 cycles as determined by the investigator. Assessment of tumor status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter. The major efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. An additional efficacy outcome measure was OS.

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55% age 65 or older; 79% White, 9% Black, and 3% Asian; 5% Hispanic or Latino; 64% ECOG PS of 0, 33% ECOG PS of 1, and 3% ECOG PS of 2; 61% had recurrent disease and 39% had primary or persistent disease; 5% received prior adjuvant chemotherapy and 43% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (81%), adenocarcinoma NOS (11%), serous carcinoma (2%), and other (6%).

The pMMR population characteristics were: median age of 66 years (range: 29 to 94), 54% age 65 or older; 72% White, 16% Black, and 5% Asian; 6% Hispanic or Latino; 67% ECOG PS of 0, 30% ECOG PS of 1, and 3% ECOG PS of 2; 56% had recurrent disease and 44% had primary or persistent disease; 26% received prior adjuvant chemotherapy and 41% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (52%), serous carcinoma (26%), adenocarcinoma NOS (10%), clear cell carcinoma (7%), and other (5%).

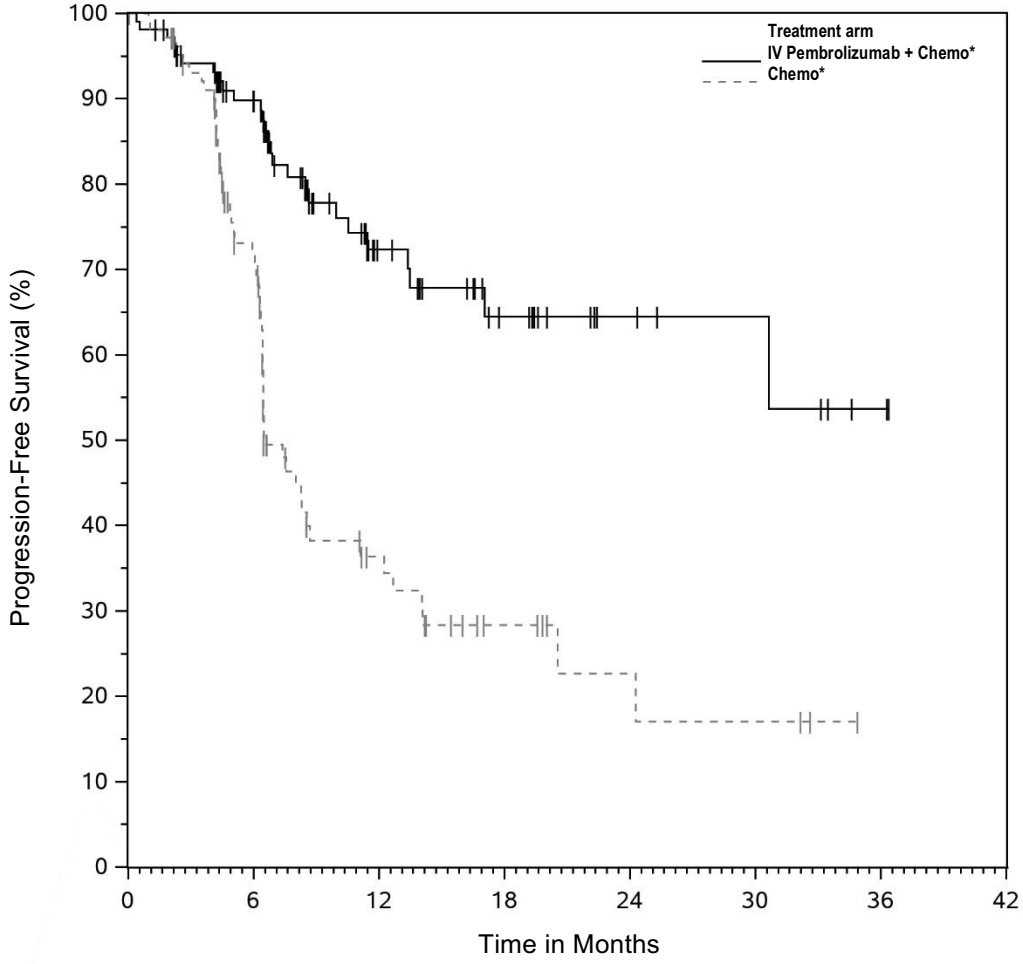
The trial demonstrated statistically significant improvements in PFS for patients randomized to intravenous pembrolizumab in combination with paclitaxel and carboplatin compared to placebo in combination with paclitaxel and carboplatin in both the dMMR and pMMR populations. Table 102 and Figures 41 and 42 summarize the efficacy results for KEYNOTE-868 by MMR status. At the time of the PFS analysis, OS data were not mature with 12% deaths in the dMMR population and 17% deaths in the pMMR population.

Table 102: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	Intravenous Pembrolizumab with paclitaxel and carboplatin n=110	Placebo with paclitaxel and carboplatin n=112	Intravenous Pembrolizumab with paclitaxel and carboplatin n=294	Placebo with paclitaxel and carboplatin n=294
PFS*				
Number (%) of patients with event	26 (24%)	57 (51%)	91 (31%)	124 (42%)
Median in months (95% CI)	NR (30.7, NR)	6.5 (6.4, 8.7)	11.1 (8.7, 13.5)	8.5 (7.2, 8.8)
Hazard ratio† (95% CI)	0.30 (0.19, 0.48)		0.60 (0.46, 0.78)	
p-Value‡	<0.0001		<0.0001	

* Based on interim PFS analysis; the information fractions for interim analyses were 49% for dMMR and 55% for pMMR.
† Based on the stratified Cox proportional hazard model
‡ Based on the stratified log-rank test
NR = not reached

Figure 41: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)

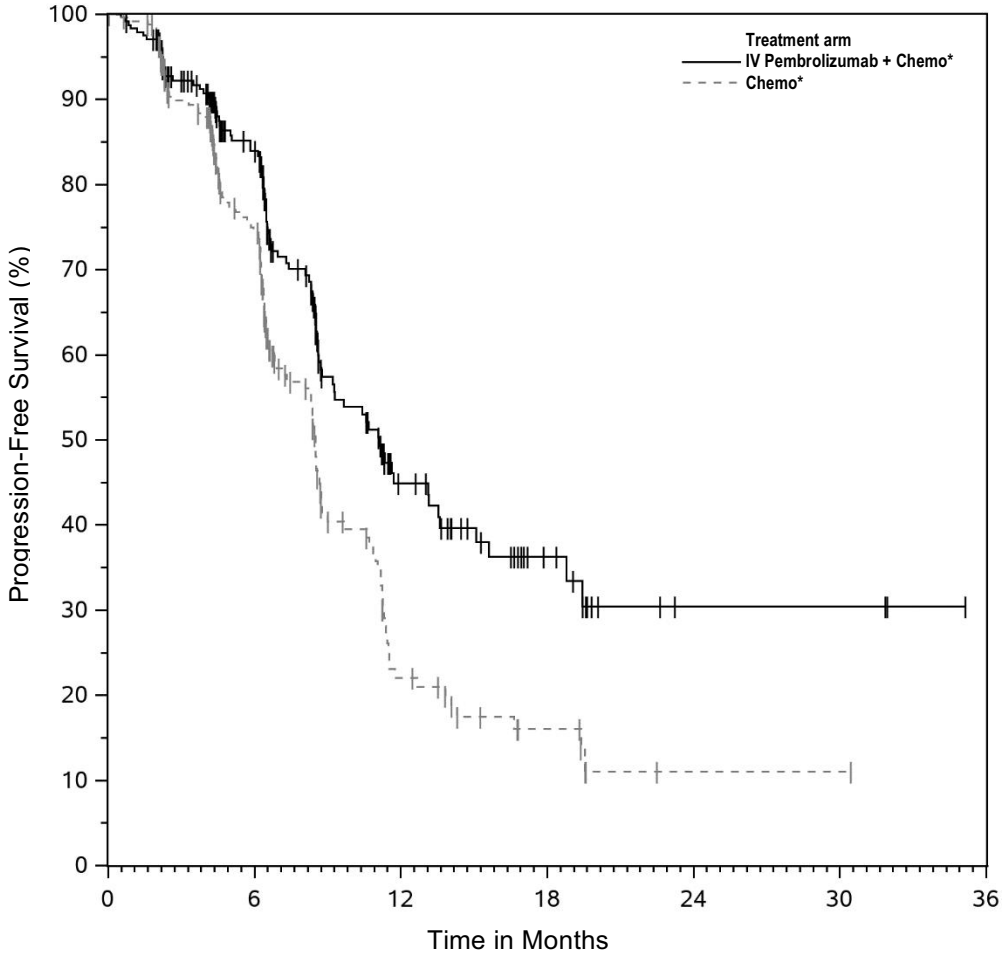


Number at Risk

IV Pembrolizumab + Chemo*	110	78	33	17	8	6	2	0
Chemo*	112	58	18	8	4	3	0	0

*Chemotherapy (paclitaxel and carboplatin)

Figure 42: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



Number at Risk							
IV Pembrolizumab + Chemo*	294	140	36	14	3	3	0
Chemo*	294	126	22	8	1	1	0

*Chemotherapy (paclitaxel and carboplatin)

Lack of Effectiveness for Adjuvant Treatment of Patients with Endometrial Carcinoma

The efficacy of intravenous pembrolizumab in combination with carboplatin and paclitaxel, with or without radiation, was investigated in KEYNOTE-B21 (NCT04634877), a randomized, multicenter, double-blind, placebo-controlled trial in 1,095 patients with newly-diagnosed, high-risk endometrial cancer with no evidence of disease on imaging following curative intent surgery. High-risk disease was defined as any of the following (staging per FIGO 2009): Stage I/II with myometrial invasion and either non-endometrioid histology or aberrant p53 expression or p53 mutation, or Stage III/IVA. The trial did not meet the prespecified primary endpoint for investigator-assessed DFS, with a HR of 1.02 (95% CI: 0.79, 1.32).

In Combination with Lenvatinib for the Treatment of Advanced Endometrial Carcinoma That Is pMMR or Not MSI-H

The efficacy of intravenous pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-775 (NCT03517449), a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients

with endometrial carcinoma that were pMMR (using the VENTANA MMR RxDx Panel test) or not MSI-H were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- Intravenous pembrolizumab 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- Investigator's choice, consisting of either doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 given weekly, 3 weeks on/1 week off.

Treatment with intravenous pembrolizumab and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for intravenous pembrolizumab, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR and DoR, as assessed by BICR.

Among the 697 pMMR patients, 346 patients were randomized to intravenous pembrolizumab in combination with lenvatinib, and 351 patients were randomized to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The pMMR population characteristics were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

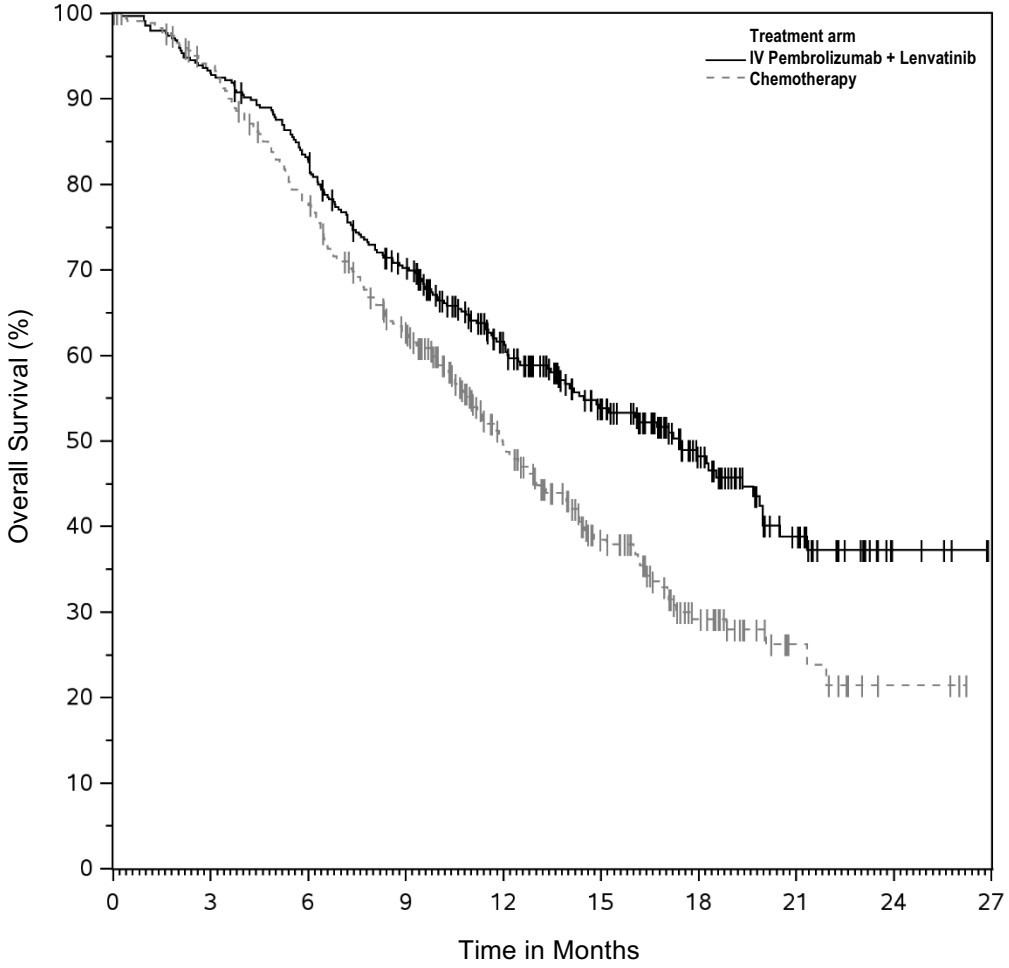
Efficacy results for the pMMR or not MSI-H patients are summarized in Table 103 and Figures 43 and 44.

Table 103: Efficacy Results in KEYNOTE-775

	Endometrial Carcinoma (pMMR or not MSI-H)	
Endpoint	**Intravenous Pembrolizumab 200 mg every 3 weeks and Lenvatinib n=346**	**Doxorubicin or Paclitaxel n=351**
OS		
Number (%) of patients with event	165 (48%)	203 (58%)
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
Hazard ratio* (95% CI)	0.68 (0.56, 0.84)	
p-Value†	0.0001	
PFS		
Number (%) of patients with event	247 (71%)	238 (68%)
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
Hazard ratio* (95% CI)	0.60 (0.50, 0.72)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	30% (26, 36)	15% (12, 19)
Complete response rate	5%	3%
Partial response rate	25%	13%
p-Value§	<0.0001	
Duration of Response	n=105	n=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

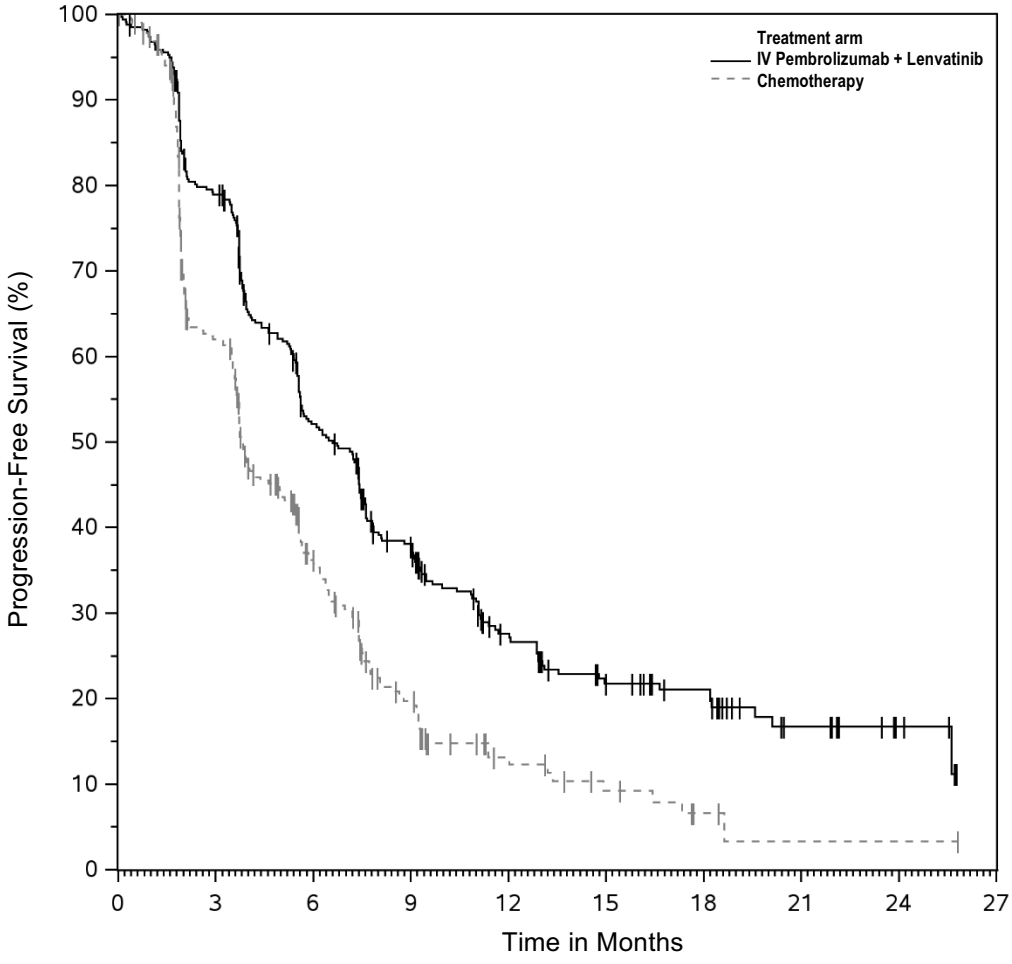
* Based on the stratified Cox regression model
† Based on stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation

Figure 43: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775 (pMMR or Not MSI-H)



Number at Risk										
IV Pembrolizumab + Lenvatinib	346	322	285	232	160	109	62	28	5	0
Chemotherapy	351	319	262	201	120	70	33	11	3	0

Figure 44: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775 (pMMR or Not MSI-H)



Number at Risk										
IV Pembrolizumab + Lenvatinib	346	264	165	112	60	39	30	12	5	0
Chemotherapy	351	177	83	37	15	8	3	1	1	0

As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

The efficacy of intravenous pembrolizumab was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received intravenous pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with intravenous pembrolizumab without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 90 patients evaluated, the baseline characteristics were: median age of 64 years (range: 42 to 86); 83% White, 8% Asian, and 3% Black; 12% Hispanic or Latino; 39% ECOG PS of 0 and 61% ECOG PS of 1; 96% had M1 disease and 4% had M0 disease at study entry; and 51% had one and 48% had

two or more prior lines of therapy. Nine patients received only adjuvant therapy and one patient received only neoadjuvant and adjuvant therapy before participating in the study.

Efficacy results are summarized in Table 104.

Table 104: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158

Endpoint	Intravenous Pembrolizumab n=90*
Objective Response Rate	
ORR (95% CI)	46% (35, 56)
Complete response rate	12%
Partial response rate	33%
Duration of Response	n=41
Median in months (range)	NR (2.9, 55.7+)
% with duration ≥12 months	68%
% with duration ≥24 months	44%

* Median follow-up time of 16.0 months (range: 0.5 to 62.1 months)
\+ Denotes ongoing response
NR = not reached

14.18 Tumor Mutational Burden-High Cancer

The efficacy of intravenous pembrolizumab was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with high tumor mutation burden (TMB-H) who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). The trial excluded patients who previously received an anti-PD-1 or other immune-modulating monoclonal antibody, or who had an autoimmune disease, or a medical condition that required immunosuppression. Patients received intravenous pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Assessment of tumor status was performed every 9 weeks for the first 12 months and every 12 weeks thereafter.

The statistical analysis plan pre-specified ≥10 and ≥13 mutations per megabase using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The major efficacy outcome measures were ORR and DoR in patients who received at least one dose of intravenous pembrolizumab as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

In KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ≥10 mutations per megabase. Among the 102 patients with TMB-H advanced solid tumors, the study population characteristics were: median age of 61 years (range: 27 to 80), 34% age 65 or older; 34% male; 81% White; and 41% ECOG PS of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

Efficacy results are summarized in Tables 105 and 106.

Table 105: Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks	
	TMB ≥10 mut/Mb n=102*	TMB ≥13 mut/Mb n=70
Objective Response Rate		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
Duration of Response	n=30	n=26
Median in months (range)†	NR (2.2+, 34.8+)	NR (2.2+, 34.8+)
% with duration ≥12 months	57%	58%
% with duration ≥24 months	50%	50%

* Median follow-up time of 11.1 months
† From product-limit (Kaplan-Meier) method for censored data
\+ Denotes ongoing response
NR = not reached

Table 106: Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	18.8+
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		(8.2, 33.2+)
Mesothelioma cancer	1	PD		

* No TMB-H patients were identified in the cholangiocarcinoma cohort
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

In an exploratory analysis in 32 patients enrolled in KEYNOTE-158 whose cancer had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI: 4%, 29%), including two complete responses and two partial responses.

14.19 Cutaneous Squamous Cell Carcinoma

The efficacy of intravenous pembrolizumab was investigated in patients with recurrent or metastatic cSCC or locally advanced cSCC enrolled in KEYNOTE-629 (NCT03284424), a multicenter, multi-cohort, non-randomized, open-label trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received intravenous pembrolizumab 200 mg intravenously every 3 weeks until documented disease progression, unacceptable toxicity, or a maximum of 24 months. Patients with initial radiographic disease progression could receive additional doses of intravenous pembrolizumab during confirmation of progression unless disease progression was symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumor status was performed every 6 weeks during the first year, and every 9 weeks during the second year. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 105 patients with recurrent or metastatic cSCC treated, the study population characteristics were: median age of 72 years (range: 29 to 95), 71% age 65 or older; 76% male;

70% White, 25% race unknown; 34% ECOG PS of 0 and 66% ECOG PS of 1. Forty-five percent of patients had locally recurrent only cSCC, 24% had metastatic only cSCC, and 31% had both locally recurrent and metastatic cSCC. Eighty-seven percent received one or more prior lines of therapy; 73% received prior radiation therapy.

Among the 54 patients with locally advanced cSCC treated, the study population characteristics were: median age of 76 years (range: 35 to 95), 80% age 65 or older; 72% male; 83% White, 13% race unknown; 41% ECOG PS of 0 and 59% ECOG PS of 1. Twenty-two percent received one or more prior lines of therapy; 63% received prior radiation therapy.

Efficacy results are summarized in Table 107.

Table 107: Efficacy Results in KEYNOTE-629

Endpoint	Intravenous Pembrolizumab Recurrent or Metastatic cSCC n=105	Intravenous Pembrolizumab Locally Advanced cSCC n=54
Objective Response Rate		
ORR (95% CI)	35% (26, 45)	52% (38, 66)
Complete response rate	12%	22%
Partial response rate	23%	30%
Duration of Response*	n=37	n=28
Median in months (range)	NR (2.7, 64.2+)	47.2 (1.0+, 49.9+)
% with duration ≥6 months	76%	89%
% with duration ≥12 months	68%	75%

* Median follow-up time: recurrent or metastatic cSCC: 23.8 months; locally advanced cSCC: 48.0 months

\+ Denotes ongoing response

14.20 Triple-Negative Breast Cancer

Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The efficacy of intravenous pembrolizumab in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with intravenous pembrolizumab as a single agent was investigated in KEYNOTE-522 (NCT03036488), a randomized (2:1), multicenter, double-blind, placebo-controlled trial conducted in 1174 patients with newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement). Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

Patients were randomized (2:1) to one of the following two treatment arms; all study medications were administered intravenously:

- **Arm 1:**
  - Four cycles of preoperative intravenous pembrolizumab 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

        -or-
      - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

        -and-
    - Paclitaxel 80 mg/m^2 every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

- Followed by four additional cycles of preoperative intravenous pembrolizumab 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
    - Doxorubicin 60 mg/m^2 ***-or-*** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen ***-and-***
    - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, nine cycles of intravenous pembrolizumab 200 mg every 3 weeks were administered.

- **Arm 2:**
    - Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
        - Carboplatin
            - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

              -or-
            - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

              -and-
        - Paclitaxel 80 mg/m^2 every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
    - Followed by four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
        - Doxorubicin 60 mg/m^2 ***-or-*** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen ***-and-***
        - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
    - Following surgery, nine cycles of placebo every 3 weeks were administered.

The trial was not designed to isolate the effect of intravenous pembrolizumab in each phase (neoadjuvant or adjuvant) of treatment.

The main efficacy outcomes were pCR rate and EFS. pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome was overall survival (OS).

The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 4.5% Black, and 1.8% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumor 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall Stage II and 25% were Stage III.

Statistically significant improvements in pCR, EFS, and OS were demonstrated at pre-specified interim analyses for patients randomized to intravenous pembrolizumab in combination with chemotherapy followed by intravenous pembrolizumab as a single agent compared with patients randomized to placebo in combination with chemotherapy followed by placebo alone.

Table 108 and Figures 45 and 46 summarize the efficacy results for KEYNOTE-522.

Table 108: Efficacy Results in KEYNOTE-522

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy/Intravenous Pembrolizumab n=784	Placebo with chemotherapy/Placebo n=390
pCR (ypT0/Tis ypN0)*		
Number of patients with pCR	494	217
pCR rate (%), (95% CI)	63.0 (59.5, 66.4)	55.6 (50.6, 60.6)
Treatment difference (%) estimate (95% CI)[†,‡]	7.5 (1.6, 13.4)	
EFS		
Number of patients with event (%)	123 (16%)	93 (24%)
Hazard ratio (95% CI)[§]	0.63 (0.48, 0.82)	
p-Value[¶,#]	0.00031	
OS		
Number of patients with event (%)	115 (15%)	85 (22%)
Hazard ratio (95% CI)[§]	0.66 (0.50, 0.87)	
p-Value[#,Þ]	0.00150	

* Based on the entire intention-to-treat population n=1174 patients

† Based on a pre-specified pCR interim analysis in n=602 patients, the pCR rate difference was statistically significant (p=0.00055 compared to a significance level of 0.003).

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

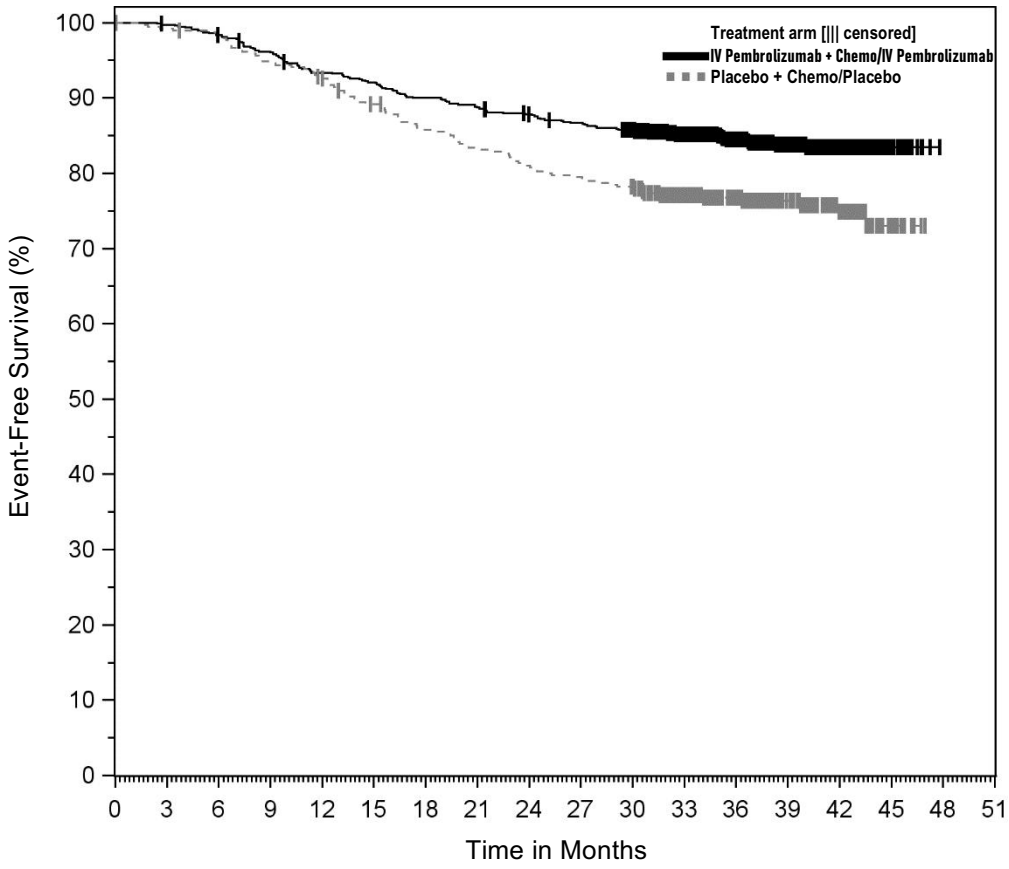
§ Based on stratified Cox regression model

¶ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052)

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

Þ Based on a pre-specified OS interim analysis (compared to a significance level of 0.0050)

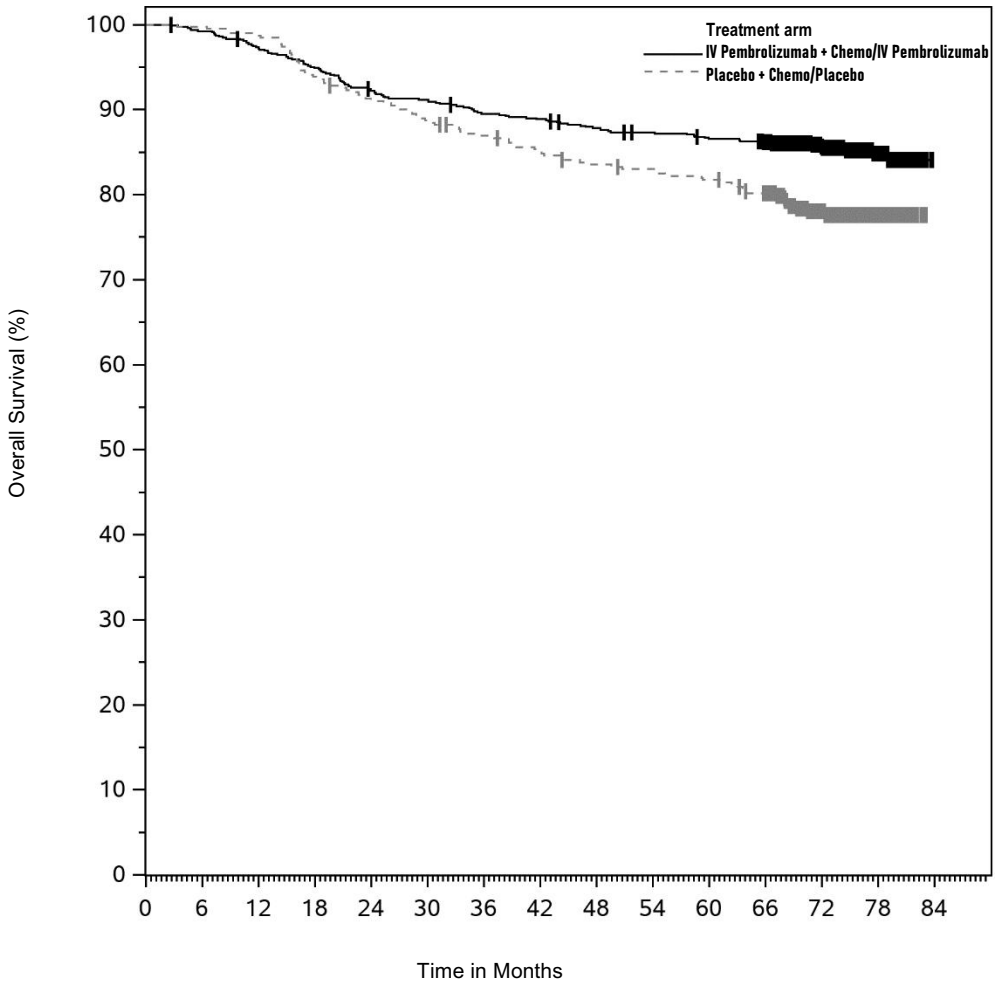
Figure 45: Kaplan-Meier Curve for Event-Free Survival in KEYNOTE-522



Number at Risk

IV Pembrolizumab + Chemo/IV Pembrolizumab	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + Chemo/Placebo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Figure 46: Kaplan-Meier Curve for Overall Survival in KEYNOTE-522



Number at Risk

IV Pembrolizumab + Chemo/IV Pembrolizumab	784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
Placebo + Chemo/Placebo	390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

Unresectable Locally Advanced or Metastatic TNBC for Tumors Expressing PD-L1 (CPS≥ 10)

The efficacy of intravenous pembrolizumab in combination with sacituzumab govitecan-hziy was evaluated in KEYNOTE-D19 (NCT05382286), a multicenter, open-label, randomized, active-controlled trial that enrolled 443 patients with unresectable locally advanced or metastatic TNBC, who had not been previously treated with systemic therapy for advanced disease and whose tumors express PD-L1 expression (CPS ≥10) according to the PD-L1 IHC 22C3 pharmDx assay. Patients may have received chemotherapy with or without a PD-1 or PD-L1 inhibitor and/or radiotherapy in early-stage TNBC; however, at least 6 months must have elapsed between the completion of systemic breast cancer therapy or surgery, whichever occurred last, and first local or distant recurrence. 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 treatment-free interval (*de novo* vs. recurrent disease within 6 to 12 months from completion of treatment in the curative setting vs. recurrent disease occurring more than 12 months from completion of treatment in the curative setting), geographic region (US/Canada/Western Europe vs. Rest of World), and prior exposure to PD-1 or PD-L1 inhibitor (yes vs. no).

Patients were randomized (1:1) to receive one of the following treatment arms; all study medications were administered via intravenous infusion:

- Intravenous pembrolizumab 200 mg on Day 1 every 3 weeks in combination with sacituzumab govitecan-hziy 10 mg/kg on Days 1 and 8 every 21 days.
- Intravenous pembrolizumab 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Assessment of tumor status was performed every 8 weeks for the first 18 months, and every 12 weeks thereafter. Treatment beyond BICR-verified disease progression per RECIST 1.1 was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Crossover to sacituzumab govitecan-hziy monotherapy was offered following disease progression and study treatment discontinuation.

The primary efficacy outcome measure was PFS as assessed by BICR according to RECIST v1.1. Additional efficacy outcome measures were OS and ORR as assessed by BICR using RECIST v1.1.

The median age was 55 years (range: 23 to 88); 26% age 65 or older, 100% female; 58% White, 24% Asian, 6% American Indian or Alaska Native, 5% Black, and 7% not specified; 29% Hispanic/Latino, 69% non-Hispanic/non-Latino and 2.0% not specified; and 70% ECOG PS of 0, 30% ECOG PS of 1, and 0.2% ECOG PS of 2; and 34% presented with *de novo* metastatic disease at screening, 18% with recurrent disease within 6 to 12 months; 48% with recurrent disease >12 months. Sixty-five percent of patients had visceral metastasis at baseline and 3% had previously treated brain metastases.

The trial demonstrated a statistically significant improvement in PFS. The OS data were immature and a total of 203 (46%) had died across both study arms.

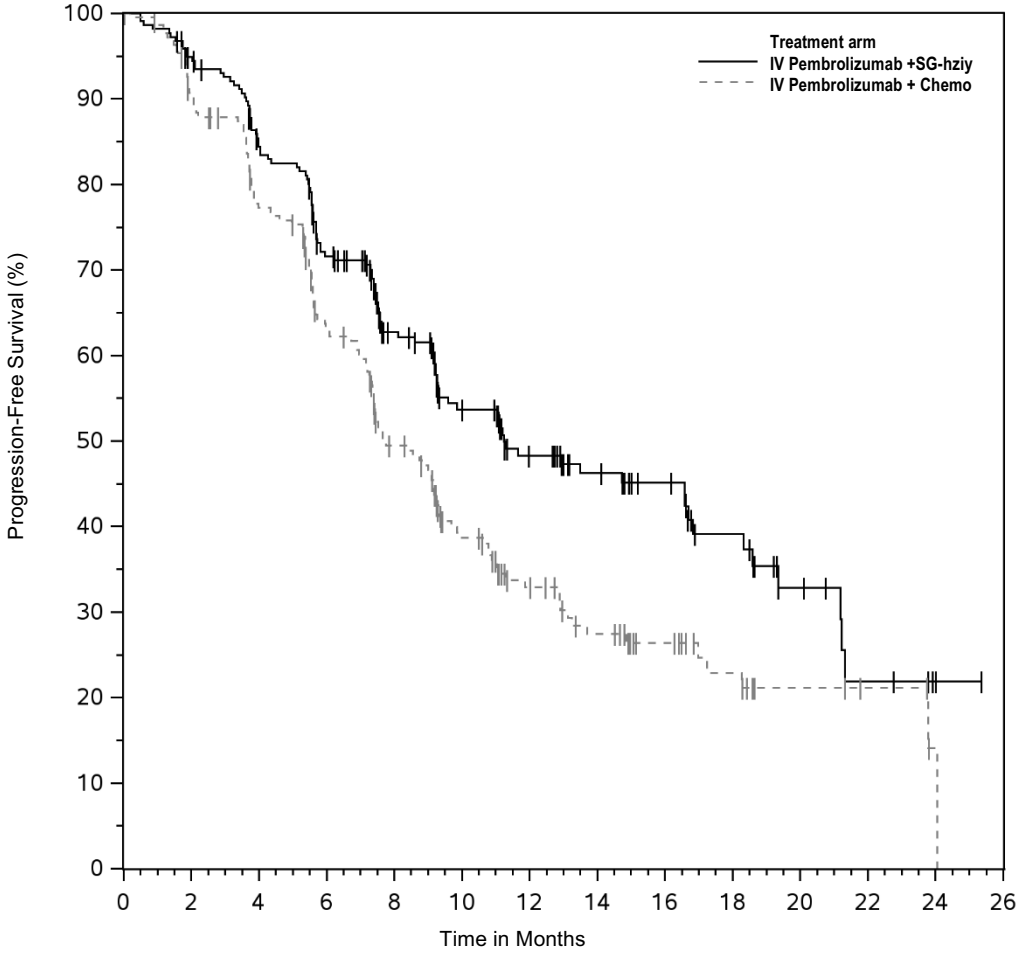
Table 109 and Figure 47 summarize the efficacy results for KEYNOTE-D19.

Table 109: Efficacy Results in KEYNOTE-D19

Endpoint	**Intravenous pembrolizumab plus Sacituzumab Govitecan-hziy n=221**	**Intravenous pembrolizumab plus chemotherapy* n=222**
PFS†		
Number of patients with event (%)	109 (49%)	140 (63%)
Median in months (95% CI)	11.2 (9.3, 16.7)	7.8 (7.3, 9.3)
Hazard ratio‡ (95% CI)	0.65 (0.51, 0.84)	
p-Value§	0.0009	
Objective Response Rate†		
ORR, (95% CI)	61% (55, 68)	55% (48, 62)
Complete Response	12%	8%
Partial Response	50%	47%

* Chemotherapy: paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin
† Assessed by BICR using RECIST 1.1
‡ Based on the stratified Cox proportional hazards model
§ Two-sided p-Value based on stratified log-rank test.

Figure 47: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-D19



Number at Risk

IV Pembrolizumab + SG-hziy	221	202	174	142	105	78	58	42	34	22	11	6	2	0
IV Pembrolizumab + Chemo	222	191	159	123	88	59	40	29	21	13	7	4	1	0

Locally Recurrent Unresectable or Metastatic TNBC for Tumors Expressing PD-L1 (CPS≥ 10)

The efficacy of intravenous pembrolizumab in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial conducted in 847 patients with locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, who had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by chemotherapy treatment (paclitaxel or paclitaxel protein-bound vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS ≥1 vs. CPS <1) according to the PD-L1 IHC 22C3 pharmDx assay, 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:

- Intravenous pembrolizumab 200 mg on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m^2 on Days 1, 8, and

15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

- Placebo on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, tested in the subgroup of patients with CPS ≥10. Additional efficacy outcome measures were ORR and DoR as assessed by BICR.

The study population characteristics for patients were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of patients had tumor PD-L1 expression CPS ≥1 and 38% had tumor PD-L1 expression CPS ≥10.

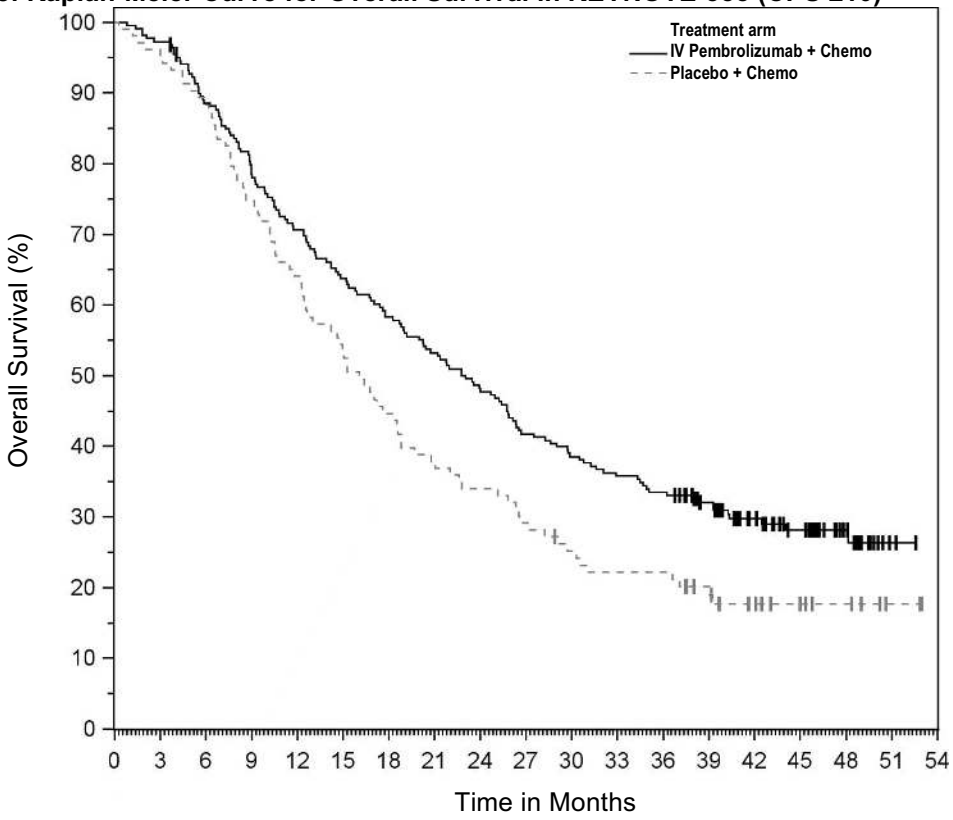
Table 110 and Figures 48 and 49 summarize the efficacy results for KEYNOTE-355.

Table 110: Efficacy Results in KEYNOTE-355 (CPS ≥10)

Endpoint	Intravenous Pembrolizumab 200 mg every 3 weeks with chemotherapy n=220	Placebo every 3 weeks with chemotherapy n=103
OS*		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio† (95% CI)	0.73 (0.55, 0.95)	
p-Value‡	0.0093	
PFS§		
Number of patients with event (%)	136 (62%)	79 (77%)
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
Hazard ratio† (95% CI)	0.65 (0.49, 0.86)	
p-Value¶	0.0012	
Objective Response Rate (Confirmed)*		
ORR (95% CI)	53% (46, 59)	41% (31, 51)
Complete response rate	17%	14%
Partial response rate	35%	27%
Duration of Response*	**n=116**	**n=42**
Median in months (95% CI)	12.8 (9.9, 25.9)	7.3 (5.5, 15.4)

* Based on the pre-specified final analysis
† Based on stratified Cox regression model
‡ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.0113)
§ Based on a pre-specified interim analysis
¶ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.00411)

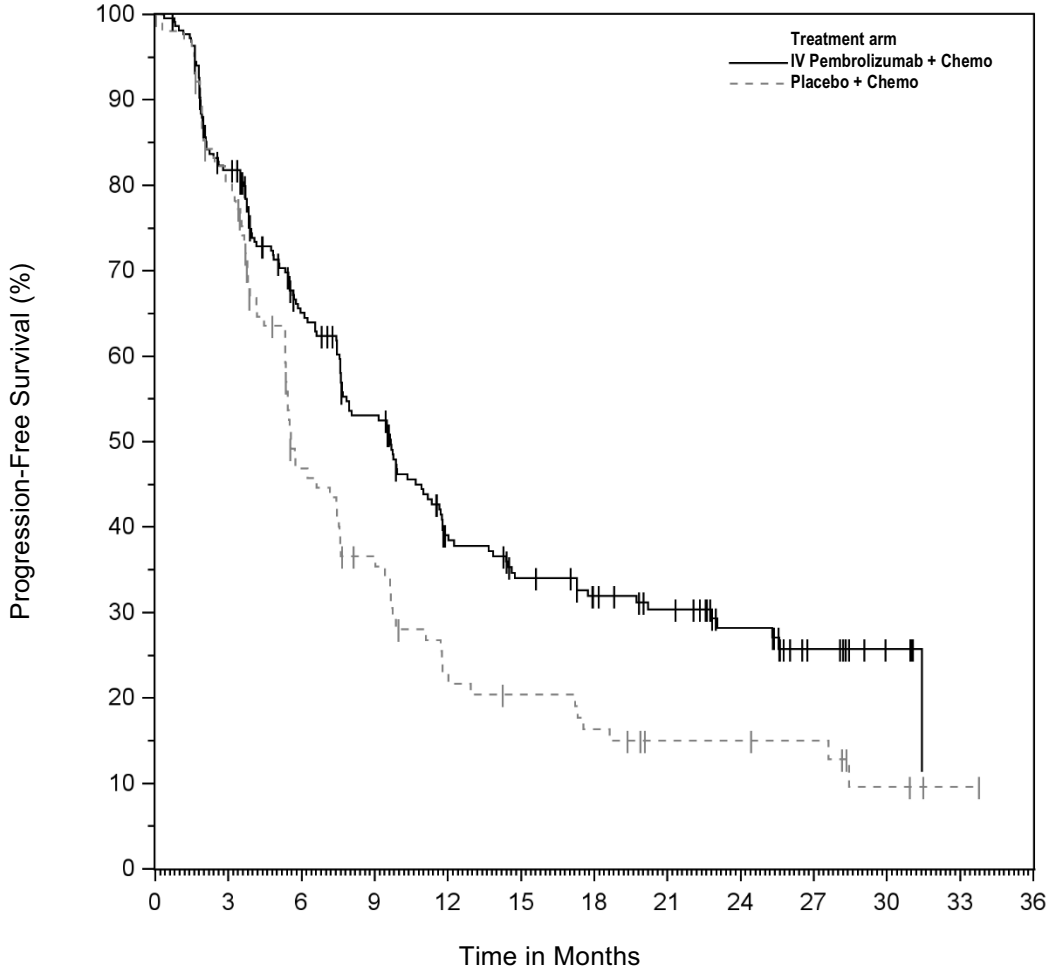
Figure 48: Kaplan-Meier Curve for Overall Survival in KEYNOTE-355 (CPS ≥10)



Number at Risk

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

Figure 49: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS ≥10)



Number at Risk													
IV Pembrolizumab + Chemo	220	173	122	96	63	52	44	37	25	12	5	0	0
Placebo + Chemo	103	80	41	30	18	15	12	8	8	7	3	1	0

14.21 Ovarian Cancer

The efficacy of intravenous pembrolizumab in combination with paclitaxel, with or without bevacizumab, was evaluated in KEYNOTE-B96 (NCT05116189), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 643 patients with platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who received one or two prior lines of systemic therapy for ovarian carcinoma. Patients must have received at least one line of platinum-based chemotherapy for ovarian cancer with radiographic evidence of disease progression within 6 months after the last dose. Prior therapy with an anti-PD-1/PD-L1 inhibitor, PARP inhibitor, or bevacizumab was permitted. Patients were enrolled regardless of PD-L1 tumor 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 investigator decision to use bevacizumab, geographic region (U.S. or European Union or Rest of World), and PD-L1 status according to the PD-L1 IHC 22C3 pharmDx assay (CPS <1 or CPS 1 to <10 or CPS ≥10). Patients were randomized (1:1) to one of the two treatment groups:

- Intravenous pembrolizumab 400 mg every 6 weeks plus paclitaxel 80 mg/m^2 with or without bevacizumab 10 mg/kg
- Placebo every 6 weeks plus paclitaxel 80 mg/m^2 with or without bevacizumab 10 mg/kg

All study medications were administered as an intravenous infusion. Intravenous pembrolizumab 400 mg or placebo were administered on Day 1 of each 6-week treatment cycle and paclitaxel 80 mg/m^2 was administered on Days 1, 8, and 15 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomization. Bevacizumab 10 mg/kg was administered on Day 1 of a 2-week treatment cycle. Treatment with intravenous pembrolizumab continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of intravenous pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 9 weeks for the first year, followed by every 12 weeks thereafter. The major efficacy outcome measure was PFS as assessed by investigator according to RECIST v1.1. An additional efficacy outcome measure was OS.

Among the 643 patients randomized, 466 patients (72%) had tumors expressing PD-L1 with a CPS ≥1. The population characteristics of these 466 patients were: median age of 62 years (range: 37 to 85), 38% age 65 or older; 67% White, 20% Asian, 8% Missing, 3% Multiple, 2% Black, 0.4% Native Hawaiian or other Pacific Islander; 13% Hispanic or Latino; 55% and 44% ECOG performance status of 0 or 1, respectively; 73% received bevacizumab as study treatment; 36% of patients had received one prior line and 64% had received two prior lines of therapy; prior systemic therapy included: 46% with bevacizumab; 39% with a PARP inhibitor, or 3% with an anti-PD-1/PD-L1 inhibitor. The platinum-free interval following the most recent line of therapy was <3 months in 47% of patients, and 3 to 6 months in 53% of patients.

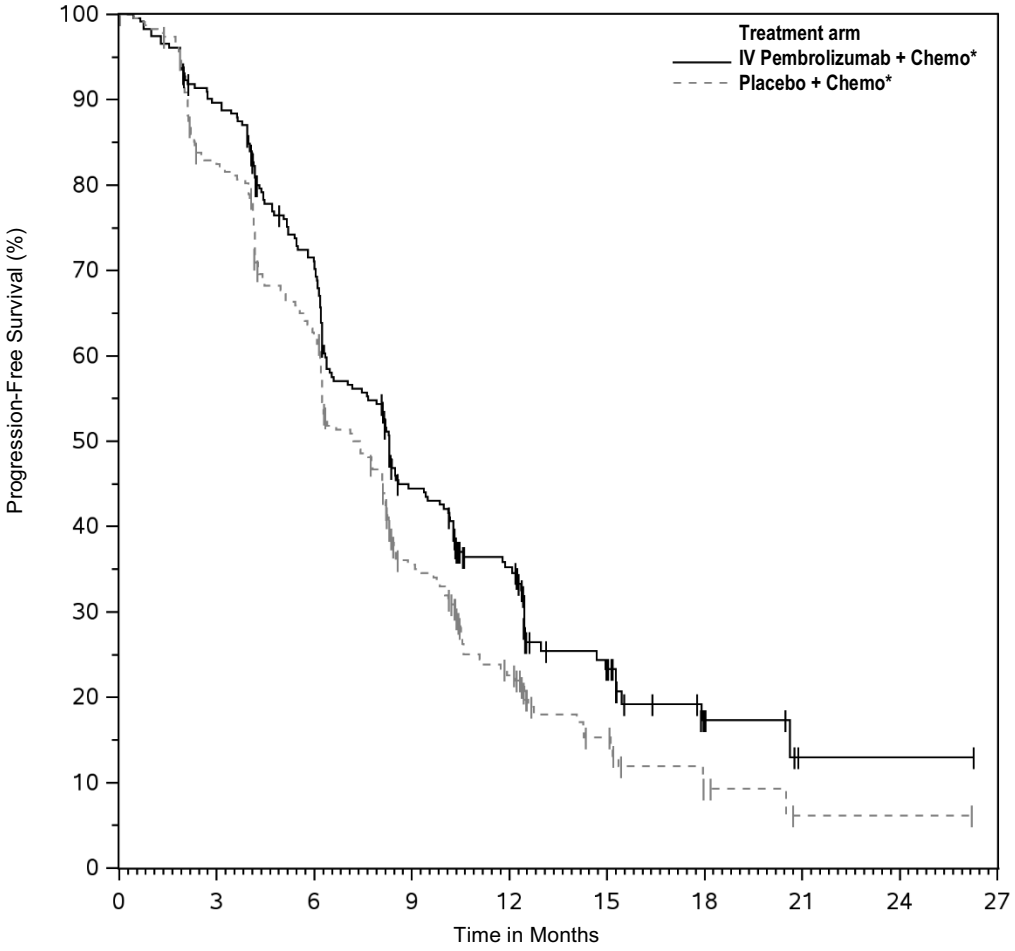
The study demonstrated statistically significant improvement in PFS and OS for patients randomized to intravenous pembrolizumab in combination with paclitaxel with or without bevacizumab compared to placebo in combination with paclitaxel with or without bevacizumab in patients whose tumors expressed PD-L1 CPS ≥1. Efficacy results are summarized in Table 111 and Figures 50 and 51.

Table 111: Efficacy Results in KEYNOTE-B96 (CPS ≥1)

Endpoint	**Intravenous pembrolizumab 400 mg every 6 weeks plus paclitaxel with or without bevacizumab** **n=234**	**Placebo** **plus paclitaxel with or without bevacizumab** **n=232**
PFS		
Number of patients with event (%)	162 (69)	180 (78)
Median in months (95% CI)	8.3 (7.0, 9.4)	7.2 (6.2, 8.1)
Hazard ratio (95% CI)	0.72 (0.58, 0.89)	
p-Value	0.0014*	
OS		
Number of patients with event (%)	157 (67)	175 (75)
Median in months (95% CI)	18.2 (15.3, 21.0)	14.0 (12.5, 16.1)
Hazard ratio (95% CI)	0.76 (0.61, 0.94)	
p-Value	0.0053†	

* Based on stratified log-rank test (p-Value [one-sided] is compared to an alpha boundary of 0.0116)
† Based on stratified log-rank test (p-Value [one-sided] is compared to an alpha boundary of 0.0083)

Figure 50: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-B96 (CPS ≥1)

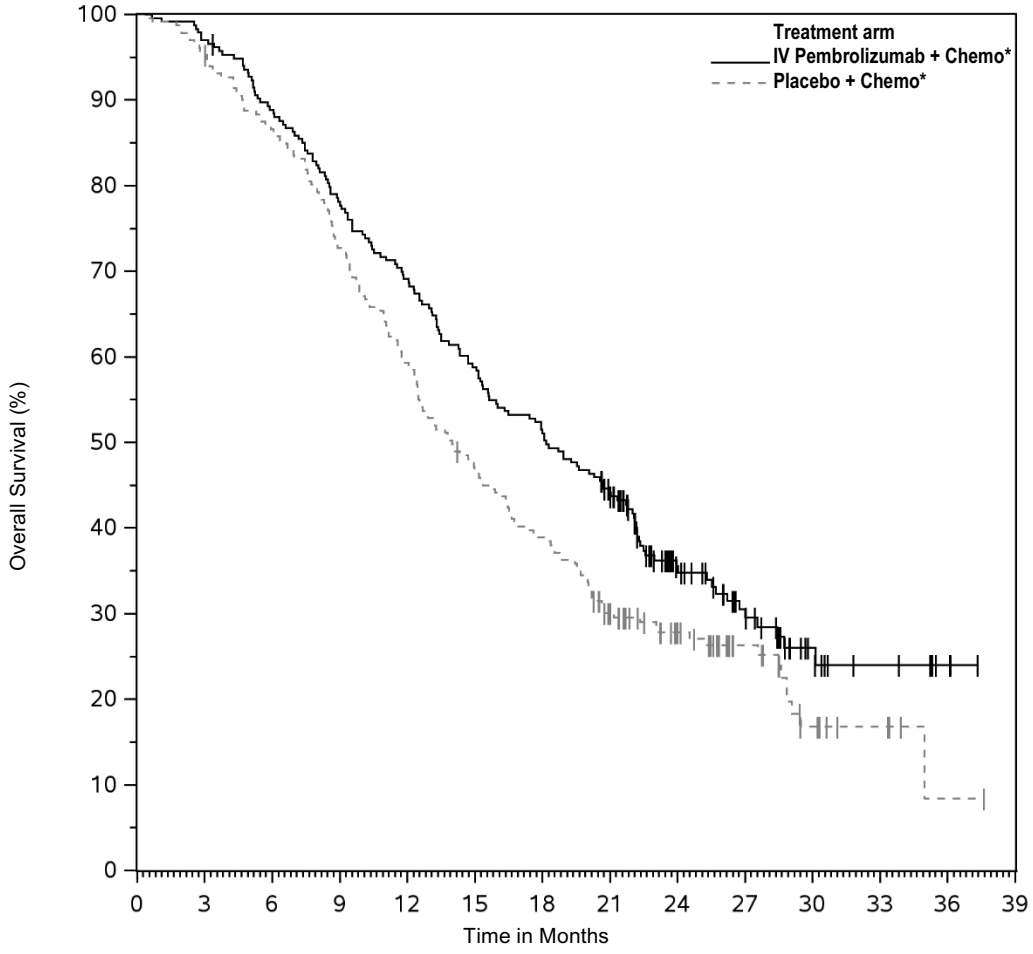


Number at Risk

IV Pembrolizumab + Chemo*	234	206	158	92	56	21	6	1	1	0
Placebo + Chemo*	232	186	138	69	36	16	5	1	1	0

*Chemotherapy (paclitaxel) with or without bevacizumab

Figure 51: Kaplan-Meier Curve for Overall Survival in KEYNOTE-B96 (CPS ≥1)



*Chemotherapy (paclitaxel) with or without bevacizumab

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA QLEX (pembrolizumab and berahyaluronidase alfa-pmph) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution supplied in single-dose vials for subcutaneous administration. Each carton contains one single-dose vial either as:

- 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa per 2.4 mL (165 mg/ 2,000 units per mL), NDC 0006-3083-01
- 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa per 4.8 mL (165 mg/ 2,000 units per mL), NDC 0006-5083-01

Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA QLEX. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
  - Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, or Type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.
  - Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)]*.
  - Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.1)]*.
  - Other immune-mediated adverse reactions:
    - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions (5.1)]*.
    - Advise patients of the risk of solid organ transplant rejection and other transplant (including corneal graft) rejection. Advise patients to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection and other transplant (including corneal graft) rejection *[see Warnings and Precautions (5.1)]*.

Hypersensitivity and Administration-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of hypersensitivity and administration-related systemic reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].*
- Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA QLEX and for 4 months after the last dose *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with KEYTRUDA QLEX and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.1)]*.

Manufactured by: Merck Sharp & Dohme LLC
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