OPDIVO QVANTIG- nivolumab and hyaluronidase-nvhy injection, solution
E.R. Squibb & Sons, L.L.C.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPDIVO QVANTIG safely and effectively. See full prescribing information for OPDIVO QVANTIG.
OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy) injection, for subcutaneous use.
Initial U.S. Approval: 2024

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2025
Dosage and Administration (2)	11/2025

INDICATIONS AND USAGE

OPDIVO QVANTIG is a combination of nivolumab, a programmed death receptor-1 (PD-1)-blocking antibody, and hyaluronidase, an endoglycosidase, indicated for the treatment of:

Renal Cell Carcinoma (RCC)

- adult patients with intermediate or poor risk advanced RCC, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab. (1.1)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of renal cell carcinoma.
- adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib. (1.1)
- adult patients with advanced RCC who have received prior anti-angiogenic therapy. (1.1)

Melanoma

- adult and pediatric (12 years and older who weigh 30 kg or greater) patients with unresectable or metastatic melanoma. (1.2)
- adult and pediatric (12 years and older who weigh 30 kg or greater) patients with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab. (1.2)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic melanoma.
- for the adjuvant treatment of adult and pediatric (12 years and older who weigh 30 kg or greater) patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. (1.3)

Non-Small Cell Lung Cancer (NSCLC)

- adult patients with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy. (1.4)
- adult patients with resectable (tumors ≥4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by OPDIVO QVANTIG monotherapy as adjuvant treatment after surgery. (1.5)
- adult patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG. (1.6)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of metastatic NSCLC.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy. (1.7)

Urothelial Carcinoma (UC)

- adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing

radical resection of UC. (1.8)
- adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine. (1.8)
- adult patients with locally advanced or metastatic UC who:
    - have disease progression during or following platinum-containing chemotherapy.
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.8)

Colorectal Cancer (CRC)

- adult and pediatric (12 years and older who weigh 30 kg or greater) patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC), following combination treatment with intravenous nivolumab and ipilimumab. (1.9)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic MSI-H or dMMR CRC.
- adult and pediatric (12 years and older who weigh 30 kg or greater) patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. (1.9)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic MSI-H or dMMR CRC.

Hepatocellular Carcinoma (HCC)

- adult patients with unresectable or metastatic HCC, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab. (1.10)
- adult patients with unresectable or metastatic HCC, who have been previously treated with sorafenib, following combination treatment with intravenous nivolumab and ipilimumab. (1.10)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic HCC.

Esophageal Cancer

- adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT). (1.11)
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy whose tumors express PD-L1 (≥1). (1.11)
    - Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of patients with unresectable advanced or metastatic ESCC.
- adult patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. (1.11)

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (≥1) in combination with fluoropyrimidine- and platinum-containing chemotherapy. (1.12)

DOSAGE AND ADMINISTRATION

- **OPDIVO QVANTIG has different dosage and administration instructions than intravenous nivolumab products.**
- **OPDIVO QVANTIG is for subcutaneous use only in the abdomen or thigh.**
- **OPDIVO QVANTIG is to be administered by a healthcare professional only. (2.1)**

OPDIVO QVANTIG is for subcutaneous use only.

- Administer by subcutaneous injection over 3 to 5 minutes. (2.3)
- Renal cell carcinoma
    - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
    - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks administered in combination with cabozantinib 40 mg once daily without food. (2.3)

- Melanoma
  - Adult and pediatric patients (12 years and older) who weigh 40 kg or greater: 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
  - Pediatric patients (12 years and older) who weigh 30 kg or greater but less than 40 kg: 300 mg/5,000 units every 2 weeks or 600 mg/10,000 units every 4 weeks. (2.3)
- Neoadjuvant treatment of resectable (tumors ≥4 cm or node positive) non-small cell lung cancer
  - 900 mg/15,000 units with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles. (2.3)
- Neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer
  - 900 mg/15,000 units with platinum-doublet chemotherapy on the same day every 3 weeks for up to 4 cycles, then continued as single-agent OPDIVO QVANTIG 1,200 mg/20,000 units every 4 weeks after surgery for up to 13 cycles (~1 year). (2.3)
- Metastatic non-small cell lung cancer
  - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
- Squamous cell carcinoma of the head and neck
  - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
- Urothelial carcinoma
  - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
- First-line unresectable or metastatic urothelial carcinoma
  - 900 mg/15,000 units every 3 weeks with cisplatin and gemcitabine on the same day for up to 6 cycles, then 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
- MSI-H or dMMR metastatic Colorectal cancer
  - Adult and pediatric patients weighing 40 kg or greater: 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
  - Pediatric patients weighing 30 kg or greater but less than 40 kg: 300 mg/5,000 units every 2 weeks or 600 mg/10,000 units every 4 weeks. (2.3)
- Hepatocellular carcinoma
  - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
- Esophageal cancer
  - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks. (2.3)
  - 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units every 4 weeks administered in combination with fluoropyrimidine- and platinum-containing chemotherapy. (2.3)
- Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
  - 600 mg/10,000 units every 2 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks. (2.3)
  - 900 mg/15,000 units every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. (2.3)
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg nivolumab and 5,000 units hyaluronidase per 2.5 mL (120 mg/2,000 units per mL) in a single-dose vial. (3)
- Injection: 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) in a single-dose vial. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions: (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, and immune-mediated nephritis and renal dysfunction.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction. (2.4)
- 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. (5.2)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.4)

ADVERSE REACTIONS

- **Most common adverse reactions (≥10%) with OPDIVO QVANTIG as monotherapy in patients with Renal Cell Carcinoma were:** musculoskeletal pain, fatigue, pruritus, rash, hypothyroidism, diarrhea, cough, and abdominal pain. (6.1)
- Safety of OPDIVO QVANTIG for the following indications is based on safety of intravenous nivolumab in these populations. The most common adverse reactions with intravenous nivolumab for these indications are presented below.
- As monotherapy for the treatment of advanced renal cell carcinoma; adjuvant treatment of completely resected Stage IIB, IIC, III, or IV melanoma; unresectable or metastatic melanoma; adjuvant treatment of NSCLC, metastatic NSCLC; squamous cell carcinoma of the head and neck; urothelial carcinoma; MSI-H or dMMR mCRC; hepatocellular carcinoma; esophageal cancer: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, vomiting, and urinary tract infection. (6.1)
- In combination with cabozantinib for the first-line treatment of advanced renal cell carcinoma: diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection. (6.1)
- In combination with platinum-doublet chemotherapy for the neoadjuvant treatment of NSCLC: nausea, constipation, fatigue, decreased appetite, and rash. (6.1)
- In combination with cisplatin and gemcitabine for the treatment of urothelial cancer: nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy. (6.1)
- In combination with fluoropyrimidine- and platinum- containing chemotherapy for the treatment of esophageal cancer and gastric cancer: nausea, peripheral neuropathy, decreased appetite, fatigue, constipation, stomatitis, diarrhea, vomiting, abdominal pain, and musculoskeletal pain. (6.1)

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

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Advanced Renal Cell Carcinoma

OPDIVO QVANTIG™, as monotherapy, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC) following treatment with intravenous nivolumab and ipilimumab combination therapy.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of renal cell carcinoma.

OPDIVO QVANTIG, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy.

1.2 Unresectable or Metastatic Melanoma

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult and pediatric patients 12 years and older who weigh 30 kg or greater with unresectable or metastatic melanoma.

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult and pediatric patients 12 years and older who weigh 30 kg or greater with unresectable or metastatic melanoma following treatment with intravenous nivolumab and ipilimumab combination therapy.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic melanoma.

1.3 Adjuvant Treatment of Melanoma

OPDIVO QVANTIG, as monotherapy, is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older who weigh 30 kg or greater with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

1.4 Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

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

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

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

1.6 Metastatic Non-Small Cell Lung Cancer

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of metastatic NSCLC.

1.7 Squamous Cell Carcinoma of the Head and Neck

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

1.8 Urothelial Carcinoma

OPDIVO QVANTIG, as monotherapy, is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

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

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic UC who:

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

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

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult and pediatric patients 12 years and older who weigh 30 kg or greater with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) following treatment with intravenous nivolumab and ipilimumab combination therapy.

OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult and pediatric patients 12 years and older who weigh 30 kg or greater, with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic MSI-H or dMMR CRC.

1.10 Hepatocellular Carcinoma

- OPDIVO QVANTIG, as monotherapy, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) following treatment with intravenous nivolumab and ipilimumab combination therapy.
- OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have been previously treated with sorafenib following treatment with intravenous nivolumab and ipilimumab combination therapy.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of patients with unresectable or metastatic HCC.

1.11 Esophageal Cancer

OPDIVO QVANTIG as monotherapy, is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).

OPDIVO QVANTIG, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1) *[see Dosage and Administration (2.2)]*.

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of patients with unresectable advanced or metastatic ESCC.

OPDIVO QVANTIG as monotherapy, is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

1.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

OPDIVO QVANTIG, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (≥1) *[see Dosage and Administration (2.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

OPDIVO QVANTIG has different dosage and administration instructions than intravenously administered nivolumab products *[see Dosage and Administration (2.5)].*

OPDIVO QVANTIG is for subcutaneous use only in the abdomen or thigh. Do not administer intravenously.

OPDIVO QVANTIG is to be administered by a healthcare professional only.

Adult patients currently receiving intravenous nivolumab as a single agent, or in combination with chemotherapy or cabozantinib, may switch to subcutaneous OPDIVO QVANTIG at their next scheduled dose.

2.2 Patient Selection

Esophageal Cancer

Select patients with unresectable advanced or metastatic ESCC for treatment with OPDIVO QVANTIG in combination with fluoropyrimidine- and platinum-containing chemotherapy based on PD-L1 expression *[see Clinical Studies (14.11)]*.

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

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

Select patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma for treatment with OPDIVO QVANTIG in combination with fluoropyrimidine-and platinum-containing chemotherapy based on PD-L1 expression *[see Clinical Studies (14.12)]*.

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

2.3 Recommended Dosage

The recommended dosages of OPDIVO QVANTIG as monotherapy are presented in Table 1.

Administer OPDIVO QVANTIG as a subcutaneous injection over 3 to 5 minutes *[see Dosage and Administration (2.5)]*.

Table 1: Recommended Dosages for OPDIVO QVANTIG as Monotherapy

Indication	**Recommended OPDIVO QVANTIG Dosage**	**Duration of Therapy**
Advanced renal cell carcinoma†	600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease progression or unacceptable toxicity
Metastatic non-small cell lung cancer		
Squamous cell carcinoma of the head and neck		
Locally advanced or metastatic urothelial carcinoma		
Hepatocellular carcinoma previously treated with sorafenib†		
Esophageal squamous cell carcinoma		
	Adult patients and pediatric	

Unresectable or metastatic melanoma†	patients age 12 years and older and weighing 40 kg or greater: 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing 30 kg or greater but less than 40 kg: 300 mg nivolumab and 5,000 units hyaluronidase every 2 weeks or 600 mg nivolumab and 10,000 units hyaluronidase every 4 weeks	
Adjuvant treatment of melanoma	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or greater: 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease recurrence or unacceptable toxicity for up to 1 year
	Pediatric patients age 12 years and older and weighing 30 kg or greater but less than 40 kg: 300 mg nivolumab and 5,000 units hyaluronidase every 2 weeks or 600 mg nivolumab and 10,000 units hyaluronidase every 4 weeks	
Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer†	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or greater: 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease progression or unacceptable toxicity, or up to 2 years
	Pediatric patients age 12 years and older and weighing 30 kg or greater but less than 40 kg:	

	300 mg nivolumab and 5,000 units hyaluronidase every 2 weeks or 600 mg nivolumab and 10,000 units hyaluronidase every 4 weeks	
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following prior treatment for metastatic disease†	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or greater: 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing 30 kg or greater but less than 40 kg: 300 mg nivolumab and 5,000 units hyaluronidase every 2 weeks or 600 mg nivolumab and 10,000 units hyaluronidase every 4 weeks	
First-line unresectable or metastatic hepatocellular carcinoma†	600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease progression or unacceptable toxicity, or up to 2 years
Adjuvant treatment of urothelial carcinoma	600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Until disease recurrence or unacceptable toxicity for up to 1 year
Adjuvant treatment of resected esophageal or gastroesophageal junction cancer		

† Dosing recommendations for monotherapy or monotherapy following intravenous nivolumab and ipilimumab combination therapy.

The recommended dosages of OPDIVO QVANTIG in combination with other therapeutic agents are presented in Table 2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO QVANTIG for the recommended dosage information, as appropriate.

Table 2: Recommended Dosages for OPDIVO QVANTIG in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO QVANTIG Dosage	Duration of Therapy
Advanced renal cell carcinoma	600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks Administer OPDIVO QVANTIG in combination with cabozantinib 40 mg orally once daily without food	OPDIVO QVANTIG: Until disease progression, unacceptable toxicity, or up to 2 years Cabozantinib: Until disease progression or unacceptable toxicity
Neoadjuvant treatment of resectable non-small cell lung cancer	900 mg nivolumab and 15,000 units hyaluronidase with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles
Neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer	Neoadjuvant: 900 mg nivolumab and 15,000 units hyaluronidase with platinum-doublet chemotherapy on the same day every 3 weeks	Neoadjuvant: in combination with platinum-doublet chemotherapy until disease progression or unacceptable toxicity, for up to 4 cycles
	Adjuvant: 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	Adjuvant: following neoadjuvant therapy and surgery, administer as a single agent until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles (up to 1 year)
First-line unresectable or metastatic urothelial carcinoma	900 mg nivolumab and 15,000 units hyaluronidase every 3 weeks Administer OPDIVO QVANTIG in combination with cisplatin and gemcitabine on the same day every 3 weeks	In combination with cisplatin and gemcitabine for up to 6 cycles
	600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks	After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose
Esophageal squamous cell carcinoma	600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks Administer OPDIVO QVANTIG in combination with fluoropyrimidine- and platinum-containing chemotherapy	Until disease progression, unacceptable toxicity, or up to 2 years
		Chemotherapy: Until disease progression or unacceptable toxicity
Gastric cancer,	600 mg nivolumab and 10,000 units hyaluronidase with fluoropyrimidine- and platinum-containing chemotherapy every 2	OPDIVO QVANTIG: Until disease progression, unacceptable

gastroesophageal junction cancer, and esophageal adenocarcinoma	weeks or 900 mg nivolumab and 15,000 units hyaluronidase with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	toxicity, or up to 2 years Chemotherapy: Until disease progression or unacceptable toxicity

2.4 Dosage Modifications

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

Dosage modifications for OPDIVO QVANTIG or OPDIVO QVANTIG in combination with other anti-cancer agents for adverse reactions that require management different from these general guidelines are summarized in Table 3 and Table 4.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity**	**Dosage Modification**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Colitis For colitis in patients treated with combination therapy with ipilimumab, see Table 4.	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy with cabozantinib, see Table 4.	AST/ALT increases to >3 and ≤8 times ULN or Total bilirubin increases to >1.5 and ≤3 times ULN.	Withhold[a]
	AST or ALT increases to >8 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Hepatitis with tumor involvement of the liver[b]	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold[a]
	AST/ALT increases to	

	>10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Endocrinopathies[c]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue

[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.
[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO QVANTIG based on recommendations for hepatitis with no liver involvement.
[c] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens-Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit of normal

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

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

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

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

2.5 Preparation and Administration

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is OPDIVO QVANTIG for subcutaneous use and NOT intravenous nivolumab. **Do NOT administer OPDIVO QVANTIG intravenously.** OPDIVO QVANTIG should be administered by a healthcare professional.

Each OPDIVO QVANTIG vial is for one-time use only. It is a ready-to-use solution for injection. It should not be diluted.

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

Preparation

No incompatibilities were observed between OPDIVO QVANTIG and polypropylene and polycarbonate syringes, or between OPDIVO QVANTIG and polyethylene, polyurethane, polyvinyl chloride, and fluorinated ethylene propylene subcutaneous administration sets.

A syringe and a transfer needle are needed to withdraw OPDIVO QVANTIG solution from the vial. OPDIVO QVANTIG may be injected subcutaneously using a 23G to 25G (3/8 to 5/8 inch) hypodermic injection needle or subcutaneous administration set (eg., winged/butterfly).

Calculate the appropriate number of vials of OPDIVO QVANTIG (300 mg/5,000 units and/or 600 mg/10,000 units) needed based on the prescribed dose.

Allow vial(s) to reach room temperature 20°C to 25°C (68°F to 77°F) before withdrawing dose.

- **300 mg nivolumab and 5,000 units hyaluronidase**
    - Withdraw 2.5 mL from the 300 mg/5,000 units vial of OPDIVO QVANTIG into the syringe.
- **600 mg nivolumab and 10,000 units hyaluronidase**
    - Withdraw 5 mL from the 600 mg/10,000 units vial of OPDIVO QVANTIG into the syringe.
- **900 mg nivolumab and 15,000 units hyaluronidase**
    - Withdraw 5 mL from the 600 mg/10,000 units vial and 2.5 mL from the 300 mg/5,000 units vial of OPDIVO QVANTIG into a single syringe for a total volume of 7.5 mL.
- **1,200 mg nivolumab and 20,000 units hyaluronidase**
    - Withdraw 5 mL from each vial of 600 mg/10,000 units OPDIVO QVANTIG into a single syringe for a total volume of 10 mL.

Select the appropriate syringe label provided in the carton that matches the prescribed dose and apply to the prepared syringe.

Discard partially used or empty vials of OPDIVO QVANTIG.

If the dose is not to be used immediately, attach a tip cap to the syringe prior to storage. To avoid clogging of the hypodermic injection needle, attach a 23G to 25G (3/8 to 5/8 inch) hypodermic injection needle to the syringe immediately prior to administration.

Storage in Syringe

Once withdrawn into the syringe, OPDIVO QVANTIG should be used immediately. If not used immediately, store the syringe:

- In the refrigerator at 2°C to 8°C (36°F to 46°F), protected from light for up to 72 hours; do not freeze, or
- At room temperature 20°C to 25°C (68°F to 77°F) for up to 8 hours. Storage at room temperature for this duration does not require protection from light.
- Discard if storage time exceeds these limits.
- If stored in the refrigerator, allow the solution to come to room temperature before administration.

Administration

- Administer the full contents of the syringe into the subcutaneous tissue of 1 of the 4 quadrants of the abdomen, or thigh over a period of 3 to 5 minutes.
- Alternate injection sites across the 4 quadrants of the abdomen or thighs for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration of OPDIVO QVANTIG is interrupted, continue administering at the same site, or at an alternate site.
- During treatment with OPDIVO QVANTIG, do not administer other subcutaneous medications at the same site used for OPDIVO QVANTIG.

3 DOSAGE FORMS AND STRENGTHS

Injection: 300 mg nivolumab and 5,000 units hyaluronidase per 2.5 mL (120 mg/2,000 units per mL), as a clear to opalescent, colorless to yellow solution in a single-dose vial.

Injection: 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL), as a clear to opalescent, colorless to yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

OPDIVO QVANTIG is a combination of 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, and an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

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

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

Withhold or permanently discontinue OPDIVO QVANTIG depending on severity *[see Dosage and Administration (2.4)]*. In general, if OPDIVO QVANTIG requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

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

Immune-Mediated Pneumonitis

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

Immune-mediated pneumonitis occurred in 2.8% (7/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.8%) and Grade 2 (2.0%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO QVANTIG in 1.6% and withholding of OPDIVO QVANTIG in 1.6% of patients.

Systemic corticosteroids were required in 100% (7/7) of patients with pneumonitis. Pneumonitis resolved in 27% of the 7 patients. Of the 4 patients in whom OPDIVO QVANTIG was withheld for pneumonitis, 2 reinitiated OPDIVO QVANTIG after symptom improvement; of these, 1 (50%) had recurrence of pneumonitis.

Immune-Mediated Colitis

OPDIVO QVANTIG can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the

definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 2.8% (7/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.4%) and Grade 2 (2.4%) adverse reactions. Colitis led to withholding of OPDIVO QVANTIG in 2.0% of patients.

Systemic corticosteroids were required in 100% (7/7) of patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 5 patients in whom OPDIVO QVANTIG was withheld for colitis, 3 reinitiated OPDIVO QVANTIG after symptom improvement; of these, 2 (67%) had recurrence of colitis.

Immune-Mediated Hepatitis and Hepatotoxicity

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

Immune-mediated hepatitis occurred in 2.4% (6/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (1.6%), and Grade 2 (0.8%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO QVANTIG in 0.8% and withholding of OPDIVO QVANTIG in 1.6% of patients.

Systemic corticosteroids were required in 100% (6/6) of patients with hepatitis. Hepatitis resolved in 67% of the 6 patients. Of the 2 patients in whom OPDIVO QVANTIG was withheld for hepatitis, 2 reinitiated OPDIVO QVANTIG after symptom improvement; of these, 1 (50%) had recurrence of hepatitis.

Intravenous Nivolumab with Cabozantinib

Nivolumab in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to nivolumab 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 nivolumab and cabozantinib and consider administering corticosteroids *[see Dosage and Administration (2.4)]*.

With the combination of intravenous nivolumab and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% (35/320) of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either intravenous nivolumab (n=11) or cabozantinib (n=9) administered as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving intravenous nivolumab, 2 patients receiving cabozantinib, and 7 patients receiving both intravenous nivolumab and cabozantinib.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

Adrenal insufficiency occurred in 2% (5/247) of patients receiving OPDIVO QVANTIG, including Grade 3 (0.8%) and Grade 2 (1.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO QVANTIG in 0.4% of patients and withholding of OPDIVO QVANTIG in 0.4% of patients.

Systemic corticosteroids were required in 100% (5/5) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 20% of the 5 patients.

Intravenous Nivolumab with Cabozantinib

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

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

Hypophysitis

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

Intravenous Nivolumab

Hypophysitis occurred in 0.6% (12/1994) of patients treated with single agent intravenous nivolumab, including Grade 3 (0.2%) and Grade 2 (0.3%). Hypophysitis led to permanent discontinuation of intravenous nivolumab in <0.1% and withholding of intravenous nivolumab in 0.2% of patients. Approximately 67% (8/12) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 42% of the 12 patients. Of the 3 patients in whom intravenous nivolumab was withheld for hypophysitis, 2 reinitiated intravenous nivolumab after symptom improvement; of these, none had recurrence of hypophysitis.

Thyroid Disorders

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

Thyroiditis

Thyroiditis occurred in 0.4% (1/247) of patients receiving OPDIVO QVANTIG, including a Grade 1 (0.4%) adverse reaction.

Systemic corticosteroids were not required in the patient with thyroiditis. Thyroiditis did not resolve in this patient.

Hyperthyroidism

Hyperthyroidism occurred in 0.8% (2/247) of patients receiving OPDIVO QVANTIG, including Grade 2 (0.4%) adverse reactions.

Systemic corticosteroids were not required in patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 2 patients.

Hypothyroidism

Hypothyroidism occurred in 9% (23/247) of patients receiving OPDIVO QVANTIG, including Grade 2 (5.7%) adverse reactions. Hypothyroidism led to withholding of OPDIVO QVANTIG in 0.8% of patients.

Systemic corticosteroids were not required in patients with hypothyroidism. Hypothyroidism resolved in 4.3% of the 23 patients. Of the 1 patient in whom OPDIVO QVANTIG was withheld for hypothyroidism, OPDIVO QVANTIG was not reinitiated after symptom improvement.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

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

Grade 3 diabetes occurred in 0.4% (1/247) of patients receiving OPDIVO QVANTIG.

No patients with diabetes required systemic corticosteroids. Diabetes did not resolve in this patient.

Immune-Mediated Nephritis with Renal Dysfunction

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

Grade 2 immune-mediated nephritis and renal dysfunction occurred in 1.2% (3/247) of patients receiving OPDIVO QVANTIG. Immune-mediated nephritis and renal dysfunction led to withholding of OPDIVO QVANTIG in 1.2% of patients.

Systemic corticosteroids were required in 100% (3/3) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 100% of the 3 patients. Of the 3 patients in whom OPDIVO QVANTIG was withheld for nephritis or renal dysfunction, 1 reinitiated OPDIVO QVANTIG after symptom improvement without recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO QVANTIG can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO QVANTIG depending on severity *[see Dosage and Administration (2.4)]*.

Immune-mediated rash occurred in 7% (17/247) of patients, including Grade 3 (0.8%) and Grade 2 (2.8%) adverse reactions. Immune-mediated rash led to withholding of OPDIVO QVANTIG in 1.2% of patients.

Systemic corticosteroids were required in 47% (8/17) of patients with immune-mediated rash. Rash resolved in 77% of the 17 patients. Of the 3 patients in whom OPDIVO QVANTIG was withheld for immune-mediated rash, all reinitiated OPDIVO QVANTIG after symptom improvement; of these, all (100%) had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

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

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

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

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

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

Endocrine: Hypoparathyroidism

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

5.2 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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

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

5.3 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO QVANTIG can cause fetal harm when administered to a pregnant woman. In animal reproduction

studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO QVANTIG and for 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

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

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

6 ADVERSE REACTIONS

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

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Complications of Allogeneic HSCT *[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 in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO QVANTIG as a single agent in 247 patients enrolled in CHECKMATE-67T, with additional data from intravenous nivolumab single-agent (1994 patients), and from intravenous nivolumab in combination with cabozantinib (320 patients) for select adverse reactions.

Advanced Renal Cell Carcinoma

CHECKMATE-67T was a multicenter, randomized, open-label study in adult patients with advanced or metastatic RCC. Patients received OPDIVO QVANTIG dose of 1,200 mg of nivolumab and 20,000 units of hyaluronidase subcutaneously every 4 weeks (n=247) or 3 mg/kg of nivolumab intravenously every 2 weeks (n=245). Among patients who received OPDIVO QVANTIG, 52% were exposed for 6 months or longer and 20% were exposed for greater than 1 year.

Serious adverse reactions occurred in 28% of patients who received OPDIVO QVANTIG. Serious adverse reactions in >1% of patients included pleural effusion (1.6%), pneumonitis (1.6%), hyperglycemia (1.2%), hyperkalemia (1.2%), hemorrhage (1.2%) and diarrhea (1.2%). Fatal adverse reactions occurred in 3 patients (1.2%) who received OPDIVO QVANTIG and included myocarditis, myositis, and colitis complications.

Permanent discontinuation of OPDIVO QVANTIG due to an adverse reaction occurred in 10% of patients. The most common adverse reaction which resulted in permanent discontinuation was pneumonitis (2%).

Dosage interruptions of OPDIVO QVANTIG due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption in >2% of patients included COVID-19 (4.5%), increased blood creatinine (2.8%), anemia, diarrhea, and fatigue (2.4% each).

The most common adverse reactions (≥10%) were musculoskeletal pain, fatigue, pruritus, rash, hypothyroidism, diarrhea, cough, and abdominal pain.

Tables 5 and 6 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-67T.

Table 5: Adverse Reactions* in ≥5% of Adult Patients with RCC Receiving OPDIVO QVANTIG in CHECKMATE-67T

Adverse Reaction	OPDIVO QVANTIG (n=247)		Intravenous Nivolumab (n=245)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	20	2.4	25	3.3
Injection site reaction[a]	8	0	0	0
Edema	5	0.4	11	0.8
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	31	1.6	39	3.3
Skin and Subcutaneous Tissue				
Pruritus	16	0.4	21	0
Rash[a]	15	1.2	13	1.2
Gastrointestinal				
Diarrhea[a]	11	0.4	14	0.4
Abdominal pain[a]	10	0	10	0.4
Nausea	8	0	9	0
Constipation	8	0	6	0
Vomiting	6	0.4	4.9	0
Respiratory, Thoracic, and Mediastinal				
Cough	11	0	11	0
Endocrine				
Hypothyroidism[a]	12	0	17	0
Metabolism and Nutrition				
Hyperglycemia	9	2.4	13	2.0
Decreased appetite	9	0	11	0.8

* Toxicity was graded per NCI CTCAE v5.
[a] Includes multiple related terms

Clinically important adverse reactions in <5% of patients who received OPDIVO QVANTIG include:

Cardiac: myocarditis

Respiratory, thoracic, and mediastinal: pneumonitis, dyspnea

Endocrine: adrenal insufficiency, hyperthyroidism, thyroiditis

Gastrointestinal: colitis, pancreatitis

Hepatobiliary: hepatitis

Nervous system: peripheral neuropathy

Skin and subcutaneous tissue: psoriasis, erythema

Musculoskeletal and connective tissue: arthritis

Blood and lymphatic system: eosinophilia

Eye disorders: uveitis

Immune system: hypersensitivity

Table 6: Laboratory Values Worsening from Baseline[a] (≥20%) in Patients with RCC Receiving OPDIVO QVANTIG in CHECKMATE-67T

Laboratory Abnormality	OPDIVO QVANTIG		Intravenous Nivolumab	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Hemoglobin decreased	46	7	48	9
Lymphocytes decreased	36	6	45	9
Chemistry				
Creatinine increased	38	1.3	43	0.4
Sodium decreased	34	2.6	40	2.5
Potassium increased	34	3.0	45	2.9
Alkaline phosphatase increased	32	2.1	33	2.0
Calcium increased	29	2.1	31	4.1
Albumin decreased	25	1.7	35	0.4
ALT increased	21	1.3	26	4.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO QVANTIG group (range: 232 to 235 patients) and intravenous nivolumab group (range: 240 to 244 patients).

Adverse Reactions in Patients Treated with Intravenous Nivolumab

The safety of OPDIVO QVANTIG for its approved indications *[see Indications and Usage (1)]* has been established in adequate and well-controlled clinical studies of intravenous nivolumab. Below is a description of adverse reactions in these adequate and well-controlled clinical studies.

First-line Renal Cell Carcinoma

CHECKMATE-214

The safety of intravenous nivolumab with ipilimumab was evaluated in CHECKMATE-214, a randomized open-label trial in 1082 patients with previously untreated advanced RCC; patients received intravenous nivolumab 3 mg/kg over 60 minutes with ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by intravenous nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (n=547) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=535) *[see Clinical*

Studies (14.1)]. The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in intravenous nivolumab and ipilimumab-treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. In this trial, 57% of patients in the intravenous nivolumab and ipilimumab arm were exposed to treatment for >6 months and 38% of patients were exposed to treatment for >1 year.

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

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

Tables 7 and 8 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of intravenous nivolumab and ipilimumab-treated patients in CHECKMATE-214.

Table 7: Adverse Reactions in >15% of Patients Receiving Intravenous Nivolumab and Ipilimumab - CHECKMATE-214

Adverse Reaction	**Intravenous Nivolumab and Ipilimumab (n=547)**		**Sunitinib (n=535)**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Adverse Reaction	99	65	99	76
General				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4	40	2.6

Arthralgia	23	1.3	16	0
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

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

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

Table 8: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on Intravenous Nivolumab and Ipilimumab - CHECKMATE-214

Laboratory Abnormality	Intravenous Nivolumab and Ipilimumab		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2	32	1
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3	64	9
Lymphopenia	36	5	63	14

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

In addition, among patients with TSH ≤ ULN at baseline, a lower proportion of patients

experienced a treatment-emergent elevation of TSH > ULN in the intravenous nivolumab and ipilimumab group compared to the sunitinib group (31% and 61%, respectively).

CHECKMATE-9ER

The safety of intravenous nivolumab with cabozantinib was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received intravenous nivolumab 240 mg over 30 minutes every 2 weeks with cabozantinib 40 mg orally once daily (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) *[see Clinical Studies (14.1)]*. Cabozantinib could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in intravenous nivolumab and cabozantinib-treated patients. In this trial, 82% of patients in the intravenous nivolumab and cabozantinib arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

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

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

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

Tables 9 and 10 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9ER.

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

Adverse Reaction	Intravenous Nivolumab and Cabozantinib (n=320)		Sunitinib (n=320)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8

Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

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

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

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

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

[h] Includes primary hypothyroidism.

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis.

Table 10: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on Intravenous Nivolumab and Cabozantinib - CHECKMATE-9ER

Laboratory Abnormality	Intravenous Nivolumab and Cabozantinib		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

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

Previously Treated Renal Cell Carcinoma

CHECKMATE-025

The safety of intravenous nivolumab was evaluated in CHECKMATE-025, a randomized open-label trial in 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received intravenous nivolumab 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.1)]*. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in intravenous nivolumab-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

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

The most frequent serious adverse reactions in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. The most

common adverse reactions (≥20%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, increased triglycerides, and hyperkalemia. In addition, among patients with TSH < ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the intravenous nivolumab group compared to the everolimus group (26% and 14%, respectively).

Tables 11 and 12 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

Table 11: Adverse Reactions in >15% of Patients Receiving Intravenous Nivolumab - CHECKMATE-025

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

Toxicity was graded per NCI CTCAE v4.

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

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

[c] Includes colitis, enterocolitis, and gastroenteritis.

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

Other clinically important adverse reactions in CHECKMATE-025 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

Investigations: weight decreased

Skin Disorders: palmar-plantar erythrodysesthesia

Table 12: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on Intravenous Nivolumab - CHECKMATE-025

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

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

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

CHECKMATE-037

The safety of intravenous nivolumab was evaluated in CHECKMATE-037, a randomized, open-label trial in 370 patients with unresectable or metastatic melanoma *[see Clinical Studies (14.2)]*. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10

mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Patients received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102): dacarbazine 1000 mg/m^2 intravenously every 3 weeks or carboplatin AUC 6 mg/mL/min and paclitaxel 175 mg/m^2 intravenously every 3 weeks. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) in intravenous nivolumab-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received intravenous nivolumab for >6 months and 3% of patients received intravenous nivolumab for >1 year.

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

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

Tables 13 and 14 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-037.

Table 13: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes rhinitis, pharyngitis, and nasopharyngitis.

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

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

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

Table 14: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037

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

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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

The safety of intravenous nivolumab was also evaluated in CHECKMATE-066, a randomized, double-blind, active-controlled trial in 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma *[see Clinical Studies (14.2)]*. The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Patients received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n=205). The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in intravenous nivolumab-treated patients. In this trial, 47% of patients received intravenous nivolumab for >6 months and 12% of patients received intravenous nivolumab for >1 year.

The trial population characteristics in the intravenous nivolumab group and dacarbazine group: 59% male, median age 65 years, 99.5% White, 61% with M1c stage disease, 74% with cutaneous melanoma, 11% with mucosal melanoma, 4% with brain metastasis, and

37% with elevated LDH at baseline. There were more patients in the intravenous nivolumab group with ECOG performance status 0 (71% vs. 59%).

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

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

Tables 15 and 16 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-066.

Table 15: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066

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

Toxicity was graded per NCI CTCAE v4.
[a] Includes periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema.
[b] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, pain in jaw, and spinal pain.
[c] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, dermatitis, allergic dermatitis, exfoliative dermatitis, acneiform dermatitis, drug eruption, and skin reaction.
[d] Includes rhinitis, viral rhinitis, pharyngitis, and nasopharyngitis.

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

Nervous System Disorders: peripheral neuropathy

Table 16: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066

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

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

CHECKMATE-067

The safety of intravenous nivolumab, administered with ipilimumab or as a single agent, was evaluated in CHECKMATE-067, a randomized (1:1:1), double-blind trial in 937 patients with previously untreated, unresectable or metastatic melanoma *[see Clinical Studies (14.2)]*. The trial excluded patients with autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

Patients were randomized to receive:

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

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

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

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

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

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

Tables 17 and 18 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

Table 17: Adverse Reactions Occurring in ≥10% of Patients on the Intravenous Nivolumab and Ipilimumab Arm or the Intravenous Nivolumab Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Adverse Reaction	Intravenous Nivolumab and Ipilimumab (n=313)		Intravenous Nivolumab (n=313)		Ipilimumab (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General						
Fatigue[a]	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1	17	1.6
Skin and Subcutaneous Tissue						
Rash[b]	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[c]	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1	16	0.3
Metabolism and Nutrition						
Decreased	29	1.9	22	0	24	1.3

appetite						
Respiratory, Thoracic and Mediastinal						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections						
Upper respiratory tract infection[d]	23	0	22	0.3	17	0
Endocrine						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular						
Hypertension[e]	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia and fatigue.

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

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

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

[e] Includes hypertension and blood pressure increased.

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

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

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

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 18: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients Treated with Intravenous Nivolumab with Ipilimumab or Single-Agent Intravenous Nivolumab and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Laboratory Abnormality	**Intravenous Nivolumab and Ipilimumab**		**Intravenous Nivolumab**		**Ipilimumab**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**

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

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

Adjuvant Treatment of Melanoma

CHECKMATE-76K

The safety of intravenous nivolumab as a single agent was evaluated in CHECKMATE-76K, a randomized (2:1), double-blind trial in 788 patients with completely resected Stage IIB/C melanoma who received intravenous nivolumab 480 mg by intravenous infusion over 30 minutes every 4 weeks (n=524) or placebo by intravenous infusion over 30 minutes every 4 weeks (n=264) for up to 1 year *[see Clinical Studies (14.3)]*. The median duration of exposure was 11 months in patients treated with intravenous nivolumab and 11 months in patients treated with placebo.

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

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

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

Tables 19 and 20 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-76K.

Table 19: Adverse Reactions Occurring in ≥10% of Patients Treated with Intravenous Nivolumab - CHECKMATE-76K

Adverse Reaction	Intravenous Nivolumab (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	36	0.4	34	0.4
Musculoskeletal and connective tissue				
Musculoskeletal pain[b]	30	0.4	26	0.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.1	15	0.4
Pruritus	20	0.2	11	0
Gastrointestinal				
Diarrhea[d]	23	1.3	16	0
Nausea	14	0	11	0
Endocrine				
Hypothyroidism[e]	14	0	2.3	0
Nervous system				
Headache[f]	12	0.2	14	0.8

Toxicity was graded per NCI CTCAE v5.

[a] Includes asthenia.

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

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

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

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

[f] Includes cluster headache, migraine.

Table 20: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients - CHECKMATE-76K

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

Potassium increased	13	1	15	1.1

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

CHECKMATE-238

The safety of intravenous nivolumab as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg by intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year (n=453) *[see Clinical Studies (14.3)]*. The median duration of exposure was 11.5 months in intravenous nivolumab-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received intravenous nivolumab for >6 months.

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

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

Tables 21 and 22 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

Table 21: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab-Treated Patients - CHECKMATE-238

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

Musculoskeletal pain[d]	32	0.4	27	0.4
Arthralgia	19	0.4	13	0.4
Nervous System				
Headache	23	0.4	31	2.0
Dizziness[e]	11	0	8	0
Infections				
Upper respiratory tract infection[f]	22	0	15	0.2
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	19	0	19	0
Dyspnea/exertional dyspnea	10	0.4	10	0.2
Endocrine				
Hypothyroidism[g]	12	0.2	7.5	0.4

Toxicity was graded per NCI CTCAE v4.
[a] Includes asthenia.
[b] Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
[c] Includes dermatitis described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.
[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.
[e] Includes postural dizziness and vertigo.
[f] Includes upper respiratory tract infection including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.
[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

Table 22: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients - CHECKMATE-238

Laboratory Abnormality	Intravenous Nivolumab		Ipilimumab 10 mg/kg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	27	0.4	12	0.9
Anemia	26	0	34	0.5
Leukopenia	14	0	2.7	0.2
Neutropenia	13	0	6	0.5
Chemistry				
Increased Lipase	25	7	23	9
Increased ALT	25	1.8	40	12
Increased AST	24	1.3	33	9
Increased Amylase	17	3.3	13	3.1
Hyponatremia	16	1.1	22	3.2
Hyperkalemia	12	0.2	9	0.5
Increased Creatinine	12	0	13	0
Hypocalcemia	10	0.7	16	0.5

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

Non-Small Cell Lung Cancer

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

CHECKMATE-816

The safety of intravenous nivolumab in combination with platinum-doublet chemotherapy was evaluated in CHECKMATE-816, a randomized, open-label, multicenter trial in patients with resectable NSCLC *[see Clinical Studies (14.4)]*. Patients received either intravenous nivolumab 360 mg administered in combination with platinum-doublet chemotherapy administered every 3 weeks for 3 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 3 cycles.

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

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

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

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

Tables 23 and 24 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-816.

Table 23: Adverse Reactions in >10% of Patients with Early-Stage NSCLC Receiving Neoadjuvant Intravenous Nivolumab and Platinum-Doublet Chemotherapy in CHECKMATE-816

Adverse Reaction	Intravenous Nivolumab and Platinum-Doublet Chemotherapy (n=176)		Platinum-Doublet Chemotherapy (n=176)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				

Nausea	38	0.6	45	1.1
Constipation	34	0	32	1.1
Vomiting	11	1.1	13	0.6
General				
Fatigue[a]	26	2.3	23	1.1
Malaise	15	0.6	14	0.6
Metabolism and Nutrition				
Decreased appetite	20	1.1	23	2.3
Skin and Subcutaneous Tissue				
Rash[b]	20	2.3	7	0
Alopecia	11	0	15	0
Nervous System				
Peripheral neuropathy[c]	13	0	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia.

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

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

Table 24: Select Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients with Early-Stage NSCLC Receiving Neoadjuvant Intravenous Nivolumab and Platinum-Doublet Chemotherapy in CHECKMATE-816

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

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

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

CHECKMATE-77T

The safety of intravenous nivolumab in combination with neoadjuvant platinum-doublet chemotherapy followed by surgery and continued adjuvant treatment with intravenous nivolumab as a single agent after surgery was evaluated in CHECKMATE-77T, a randomized, double-blind, multicenter trial in patients with previously untreated resectable Stage IIA (>4 cm) to IIIB (T3N2 or T4N2) NSCLC (per the AJCC Cancer Staging Manual 8th Edition) *[see Clinical Studies (14.5)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. The median duration of exposure to intravenous nivolumab was 10.3 months (range: 1 day to 22.3 months).

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

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

Neoadjuvant Phase of CHECKMATE-77T

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

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

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

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

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

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

Adjuvant Phase of CHECKMATE-77T

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

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

Second-line Treatment of Metastatic NSCLC

CHECKMATE-017 and CHECKMATE-057

The safety of intravenous nivolumab was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.6)]*. These trials excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received intravenous nivolumab 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m^2 intravenously every 3 weeks. The median duration of therapy in intravenous nivolumab-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received intravenous nivolumab for at least 6 months and 18% of patients received intravenous nivolumab for at least 1 year and in CHECKMATE-057, 30% of patients received intravenous nivolumab for >6 months and 20% of patients received intravenous nivolumab for >1 year.

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

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

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

Tables 25 and 26 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

Table 25: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab-

Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057

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

Toxicity was graded per NCI CTCAE v4.

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

Table 26: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Intravenous Nivolumab-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057

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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab group (range: 405 to 417 patients) and docetaxel group (range: 372 to 390 patients), except for TSH: intravenous nivolumab group n=314 and docetaxel group n=297.
[b] Not graded per NCI CTCAE v4.

Squamous Cell Carcinoma of the Head and Neck

CHECKMATE-141

The safety of intravenous nivolumab was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based

therapy *[see Clinical Studies (14.7)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously weekly). The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in intravenous nivolumab-treated patients. In this trial, 18% of patients received intravenous nivolumab for >6 months and 2.5% of patients received intravenous nivolumab for >1 year.

The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the intravenous nivolumab group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

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

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

Urothelial Carcinoma

Adjuvant Treatment of Urothelial Carcinoma (UC)

CHECKMATE-274

The safety of intravenous nivolumab was evaluated in CHECKMATE-274, a randomized, double-blind, multicenter trial of adjuvant intravenous nivolumab versus placebo in adult patients who had undergone radical resection of UC originating in the bladder or upper urinary tract (renal pelvis or ureter) and were at high risk of recurrence *[see Clinical Studies (14.8)]*. Patients received intravenous nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=351) or placebo (n=348) until recurrence or unacceptable toxicity for a maximum of 1 year. The median duration of intravenous nivolumab treatment was 8.8 months (range: 0 to 12.5).

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

patients.

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

Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-274.

Table 27: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-274

Adverse Reaction	Intravenous Nivolumab (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	36	1.7	19	0.3
Pruritus	30	0	16	0
General				
Fatigue/Asthenia	36	1.1	32	0.3
Pyrexia	10	0.3	10	0.3
Gastrointestinal				
Diarrhea[b]	30	2.8	27	1.7
Nausea	16	0.6	13	0
Abdominal pain[c]	15	0.9	15	0.6
Constipation	13	0.3	15	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	28	0.6	24	0.9
Arthralgia	11	0.3	13	0
Infections				
Urinary tract infection[e]	22	6	23	9
Upper respiratory tract infection[f]	16	0.3	16	0.6
Endocrine				
Hyperthyroidism	11	0	1.1	0
Hypothyroidism	11	0	2.3	0
Renal and Urinary Disorders				
Renal dysfunction[g]	17	1.7	16	0.9
Respiratory, Thoracic and Mediastinal				
Cough[h]	14	0	11	0
Dyspnea[i]	11	0.3	6	0.3
Metabolism and Nutrition				
Decreased appetite	13	0.9	7	0.3
Nervous System Disorders				
Dizziness[j]	11	0.3	9	0
Hepatobiliary				
Hepatitis[k]	11	4	8	0.6

Toxicity was graded per NCI CTCAE v4.

[a] Includes acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, eczema asteatotic, eczema nummular, erythema, erythema

multiforme, lichen sclerosus, lichenoid keratosis, pemphigoid, photosensitivity reaction, pigmentation disorder, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rosacea, skin exfoliation, skin lesion, skin reaction, toxic skin eruption, and urticaria.

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

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

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

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

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

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

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

[i] Includes dyspnea and exertional dyspnea.

[j] Includes dizziness, postural dizziness and vertigo.

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

Table 28: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-274

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

[a] Each test incidence is based on the number of patients who had both baseline and at

least one on-study laboratory measurement available: intravenous nivolumab group (range: 322 to 348 patients) and placebo group (range: 312 to 341 patients).

First-line Treatment of Unresectable or Metastatic UC

CHECKMATE-901

The safety of intravenous nivolumab was evaluated in CHECKMATE-901, a randomized, open-label trial in cisplatin-eligible patients with unresectable or metastatic UC *[see Clinical Studies (14.8)]*. Patients received either intravenous nivolumab 360 mg with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by single-agent intravenous nivolumab 480 mg every 4 weeks up to 2 years (n=304), or cisplatin and gemcitabine chemotherapy every 3 weeks for up to 6 cycles (n=288). Patients discontinuing cisplatin alone were permitted to switch to carboplatin.

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

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

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

Tables 29 and 30 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-901.

Table 29: Adverse Reactions Occurring in ≥10% of Treated Patients - CHECKMATE-901

Adverse Reaction	**Intravenous Nivolumab and Platinum-Doublet Chemotherapy (n=304)**		**Platinum-Doublet Chemotherapy (n=288)**	
	All Grades (%)	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Gastrointestinal disorders				
Nausea	52	0.3	53	1
Constipation	30	0	28	0.7
Vomiting	23	1.3	19	2.1
Diarrhea[a]	19	2	14	0
Abdominal pain[b]	14	0.3	9	0.3
General				
Fatigue[c]	48	3.9	43	4.2
Edema[d]	18	0	9	0.3
Pyrexia[e]	14	1	14	0

Musculoskeletal and Connective Tissue				
Musculoskeletal pain[f]	33	3	21	0.3
Metabolism and Nutrition				
Decreased appetite	30	1.6	19	1
Skin and Subcutaneous Tissue				
Rash[g]	25	2.3	7	0.3
Pruritus	17	0.7	3.5	0
Nervous System Disorders				
Peripheral neuropathy[h]	20	0.7	14	0
Headache[i]	11	0	5	0
Infections				
Urinary tract infection[j]	19	8	18	8
Endocrine disorders				
Hypothyroidism[k]	17	0	0.3	0
Renal and Urinary Disorders				
Renal dysfunction[l]	14	6	11	1.7
Hematuria	11	1	7	1.4
Investigations				
Weight decreased	11	0.3	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes colitis, immune-mediated enterocolitis.

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

[c] Includes asthenia.

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

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

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

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

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

[i] Includes occipital neuralgia.

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

[k] Includes blood stimulating hormone increased.

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

Table 30: Selected Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients - CHECKMATE-901

Laboratory Abnormality	**Intravenous Nivolumab and Platinum-Doublet Chemotherapy (n=304)**	**Platinum-Doublet Chemotherapy (n=288)**

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

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

Previously Treated Advanced or Metastatic UC

CHECKMATE-275

The safety of intravenous nivolumab was evaluated in CHECKMATE-275, a single arm trial in which 270 patients with locally advanced or metastatic UC had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.8)]*. Patients received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a dose interruption for an adverse reaction.

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

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

Tables 31 and 32 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

Table 31: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

	Intravenous Nivolumab

Adverse Reaction	(n=270)	
	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	51
General		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[a]	30	2.6
Arthralgia	10	0.7
Metabolism and Nutrition		
Decreased appetite	22	2.2
Gastrointestinal		
Nausea	22	0.7
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[b]	13	1.5
Vomiting	12	1.9
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
Infections		
Urinary tract infection/escherichia/fungal urinary tract infection	17	7
Skin and Subcutaneous Tissue		
Rash[c]	16	1.5
Pruritus	12	0
Endocrine		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

Table 32: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275

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

Hyponatremia	41	11
Increased creatinine	39	2
Increased alkaline phosphatase	33	5.5
Hypocalcemia	26	0.8
Increased AST	24	3.5
Increased lipase	20	7
Hyperkalemia	19	1.2
Increased ALT	18	1.2
Increased amylase	18	4.4
Hypomagnesemia	16	0
Hematology		
Lymphopenia	42	9
Anemia	40	7
Thrombocytopenia	15	2.4
Leukopenia	11	0

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

MSI-H or dMMR Metastatic Colorectal Cancer

First-line Treatment of MSI-H or dMMR Metastatic Colorectal Cancer (mCRC)

CHECKMATE-8HW

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

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

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

Serious adverse reactions occurred in 46% of patients receiving intravenous nivolumab in combination with ipilimumab, and 39% of patients receiving intravenous nivolumab alone. The most frequent serious adverse reactions reported in ≥1% of patients who received intravenous nivolumab with ipilimumab were adrenal insufficiency (2.8%), hypophysitis (2.8%), diarrhea (2.0%), abdominal pain (2.0%), small intestinal obstruction

(2.0%), pneumonia (1.7%), acute kidney injury (1.4%), immune mediated enterocolitis (1.4%), pneumonitis (1.4%), colitis (1.1%), large intestinal obstruction (1.1%), and urinary tract infection (1.1%). The most frequent serious adverse reactions reported in >1% of patients who received intravenous nivolumab, as a single agent, were intestinal obstruction (2.3%), acute kidney injury (1.7%), COVID-19 (1.7%), abdominal pain (1.4%), diarrhea (1.4%), ileus (1.4%), subileus (1.4%), pulmonary embolism (1.4%), adrenal insufficiency (1.1%) and pneumonia (1.1%).

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

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

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

Tables 33 and 34 summarize selected adverse reactions and selected laboratory abnormalities for intravenous nivolumab in combination with ipilimumab and the single agent intravenous nivolumab arms respectively, in CHECKMATE-8HW.

Table 33: Adverse Reactions[a] in ≥10% in Patients with a Difference Between Arms of >5% for All Grades in CHECKMATE-8HW

Adverse Reaction	Intravenous Nivolumab and Ipilimumab (n=352)		Intravenous Nivolumab (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				
Diarrhea[a]	35	4.5	30	3.4
Skin and Subcutaneous Tissue				
Pruritus	30	0	23	0
Musculoskeletal and Connective Tissue				
Arthralgia	20	0.6	15	0.6
Endocrine				
Hypothyroidism	18	0.6	10	0
Hyperthyroidism	12	0	5	0

Toxicity was graded per NCI CTCAE v5.

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

Table 34: Laboratory Values Worsening from Baseline[a] in ≥10% of Patients and a Difference Between Arms of >5% for All Grades - CHECKMATE-8HW

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

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

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

CHECKMATE-142

The safety of intravenous nivolumab administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial *[see Clinical Studies (14.9)]*. In CHECKMATE-142, 74 patients with mCRC received intravenous nivolumab 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or until intolerable toxicity and 119 patients with mCRC received intravenous nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then intravenous nivolumab 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity.

In the intravenous nivolumab with ipilimumab cohort, serious adverse reactions occurred in 47% of patients. Treatment was discontinued in 13% of patients and delayed in 45% of patients for an adverse reaction. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Tables 35 and 36 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-142. Based on the design of CHECKMATE-142, the data

below cannot be used to identify statistically significant differences between the two cohorts summarized below for any adverse reaction.

Table 35: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142

Adverse Reaction	Intravenous Nivolumab (n=74)		Intravenous Nivolumab and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	54	5	49	6
Pyrexia	24	0	36	0
Edema[b]	12	0	7	0
Gastrointestinal				
Diarrhea	43	2.7	45	3.4
Abdominal pain[c]	34	2.7	30	5
Nausea	34	1.4	26	0.8
Vomiting	28	4.1	20	1.7
Constipation	20	0	15	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	28	1.4	36	3.4
Arthralgia	19	0	14	0.8
Respiratory, Thoracic and Mediastinal				
Cough	26	0	19	0.8
Dyspnea	8	1	13	1.7
Skin and Subcutaneous Tissue				
Rash[e]	23	1.4	25	4.2
Pruritus	19	0	28	1.7
Dry Skin	7	0	11	0
Infections				
Upper respiratory tract infection[f]	20	0	9	0
Endocrine				
Hyperglycemia	19	2.7	6	1
Hypothyroidism	5	0	14	0.8
Hyperthyroidism	4	0	12	0
Nervous System				
Headache	16	0	17	1.7
Dizziness	14	0	11	0
Metabolism and Nutrition				
Decreased appetite	14	1.4	20	1.7
Psychiatric				
Insomnia	9	0	13	0.8
Investigations				
Weight decreased	8	0	10	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.
[b] Includes peripheral edema and peripheral swelling.
[c] Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.
[d] Includes back pain, pain in extremity, myalgia, neck pain, and bone pain.
[e] Includes dermatitis, dermatitis acneiform, and rash described as maculo-papular, erythematous, and generalized.
[f] Includes nasopharyngitis and rhinitis.

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

Table 36: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-142

Laboratory Abnormality	Intravenous Nivolumab (n=74)		Intravenous Nivolumab and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	50	7	42	9
Lymphopenia	36	7	25	6
Neutropenia	20	4.3	18	0
Thrombocytopenia	16	1.4	26	0.9
Chemistry				
Increased alkaline phosphatase	37	2.8	28	5
Increased lipase	33	19	39	12
Increased ALT	32	2.8	33	12
Increased AST	31	1.4	40	12
Hyponatremia	27	4.3	26	5
Hypocalcemia	19	0	16	0
Hypomagnesemia	17	0	18	0
Increased amylase	16	4.8	36	3.4
Increased bilirubin	14	4.2	21	5
Hypokalemia	14	0	15	1.8
Increased creatinine	12	0	25	3.6
Hyperkalemia	11	0	23	0.9

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

Hepatocellular Carcinoma

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

CHECKMATE-9DW

The safety of intravenous nivolumab 1 mg/kg in combination with ipilimumab was evaluated in CHECKMATE-9DW, a randomized, open-label trial in adult patients with unresectable or metastatic HCC *[see Clinical Studies (14.10)]*. Patients received intravenous nivolumab 1 mg/kg in combination with ipilimumab (n=332) or investigator's choice of lenvatinib (n=275) or sorafenib (n=50) at the following dosage:

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

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

Serious adverse reactions occurred in 53% of patients treated with intravenous nivolumab 1 mg/kg in combination with ipilimumab. The most frequent non liver-related serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab 1 mg/kg in combination with ipilimumab were diarrhea/colitis (4.5%), gastrointestinal hemorrhage (3%), and rash (2.4%).

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

Fatal adverse reactions occurred in 12 (3.6%) patients who received intravenous nivolumab 1 mg/kg in combination with ipilimumab; these included 4 (1.2%) patients who died due to immune-mediated or autoimmune hepatitis and 4 (1.2%) patients who died of hepatic failure.

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

Dosage interruptions of intravenous nivolumab 1 mg/kg due to an adverse reaction occurred in 62% of patients. Adverse reactions which required dosage interruption in >5% of patients included increased AST (13%), increased ALT (11%), and diarrhea/colitis (8%).

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

Tables 37 and 38 summarize the adverse reactions and laboratory abnormalities,

respectively, in CHECKMATE-9DW.

Table 37: Adverse Reactions Occurring in ≥10% of Intravenous Nivolumab 1 mg/kg in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	Intravenous Nivolumab 1 mg/kg and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	36	3.6	15	1.2
Pruritus	34	1.5	7	0.3
General				
Fatigue[a]	33	2.4	39	4
Pyrexia[a]	15	0.6	9	1.5
Edema[a]	13	1.2	13	1.5
Gastrointestinal				
Diarrhea[a]	25	6	39	3.4
Abdominal pain[a]	14	1.2	27	2.5
Nausea	10	0.3	16	0.9
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	17	0.6	23	0.3
Arthralgia	12	0.3	13	0.6
Metabolism and Nutrition				
Decreased appetite	16	1.2	28	1.8
Endocrine				
Hypothyroidism[a]	14	0	27	0
Hyperthyroidism	11	0.6	1.5	0
Respiratory, Thoracic and Mediastinal				
Cough[a]	13	0	8	0

Toxicity was graded per NCI CTCAE v5

[a] Represents a composite of multiple related terms.

Clinically important adverse reactions reported in <10% of patients who received intravenous nivolumab 1 mg/kg with ipilimumab were hyperglycemia (8%), adrenal insufficiency (4.2%), pneumonitis (2.7%), and pancreatitis (2.4%).

Table 38: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of intravenous Nivolumab 1 mg/kg in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	Intravenous Nivolumab 1 mg/kg and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	62	29	51	14

Increased ALT	61	17	46	9
Increased lipase	58	16	39	5
Decreased albumin	48	0.9	57	0.6
Hyponatremia	45	6	42	3.8
Hyperglycemia	44	15	32	2.1
Increased bilirubin	44	10	44	8
Increased amylase	41	6	26	1
Increased alkaline phosphatase	36	1.2	38	5
Hypocalcemia	29	0.9	46	0
Increased creatinine	26	2.4	23	0.6
Hypokalemia	21	2.1	20	2.6
Hematology				
Anemia	44	5	40	3.8
Lymphopenia	40	6.1	40	8
Thrombocytopenia	27	4	44	4.8
Neutropenia	24	4	32	3.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous nivolumab 1 mg/kg and ipilimumab group (range: 168 to 331 patients) and lenvatinib or sorafenib group (range: 145 to 315 patients).

Previously Treated Hepatocellular Carcinoma

CHECKMATE-040

The safety of intravenous nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of CHECKMATE-040, a multicenter, multiple-cohort, open-label trial *[see Clinical Studies (14.10)]* who progressed on or were intolerant to sorafenib. Intravenous nivolumab and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent intravenous nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the intravenous nivolumab and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of intravenous nivolumab and ipilimumab. During the entire treatment period, the median duration of exposure to intravenous nivolumab was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

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

Tables 39 and 40 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-040.

Table 39: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Nivolumab in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	Intravenous Nivolumab and Ipilimumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue		
Rash	53	8
Pruritus	53	4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain	41	2
Arthralgia	10	0
Gastrointestinal		
Diarrhea	39	4
Abdominal pain	22	6
Nausea	20	0
Ascites	14	6
Constipation	14	0
Dry mouth	12	0
Dyspepsia	12	2
Vomiting	12	2
Stomatitis	10	0
Respiratory, Thoracic and Mediastinal		
Cough	37	0
Dyspnea	14	0
Pneumonitis	10	2
Metabolism and Nutrition		
Decreased appetite	35	2
General		
Fatigue	27	2
Pyrexia	27	0
Malaise	18	2
Edema	16	2
Influenza-like illness	14	0
Chills	10	0
Nervous System		
Headache	22	0
Dizziness	20	0
Endocrine		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4

Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

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

Table 40: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving Intravenous Nivolumab in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

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

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

Esophageal Cancer

Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

CHECKMATE-577

The safety of intravenous nivolumab was evaluated in CHECKMATE-577, a randomized, placebo-controlled, double-blinded, multicenter trial in 792 treated patients with

completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following chemoradiotherapy (CRT) *[see Clinical Studies (14.11)]*. The trial excluded patients who did not receive concurrent CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Patients received either intravenous nivolumab 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Patients were treated until disease recurrence, unacceptable toxicity, or for up to 1-year total duration. The median duration of exposure was 10.1 months (range: <0.1 to 14 months) in intravenous nivolumab-treated patients and 9 months (range: <0.1 to 15 months) in placebo-treated patients. Among patients who received intravenous nivolumab, 61% were exposed for >6 months and 54% were exposed for >9 months.

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

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

Tables 41 and 42 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-577.

Table 41: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Nivolumab - CHECKMATE-577

Adverse Reaction	Intravenous Nivolumab (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	96	34	93	32
Gastrointestinal				
Diarrhea	29	0.9	29	0.8
Nausea	23	0.8	21	0
Abdominal Pain[a]	17	0.8	20	1.5
Vomiting	15	0.6	16	1.2
Dysphagia	13	0.8	17	3.5
Dyspepsia[b]	12	0.2	16	0.4
Constipation	11	0	12	0
General				
Fatigue[c]	34	1.3	29	1.5
Respiratory, Thoracic and Mediastinal				
Cough[d]	20	0.2	21	0.4
Dyspnea[e]	12	0.8	12	0.4
Skin and Subcutaneous Tissue				
Rash[f]	21	0.9	10	0.4
Pruritus	13	0.4	6	0
Investigations				
Weight decreased	13	0.4	9	0

Musculoskeletal and Connective Tissue				
Musculoskeletal pain[g]	21	0.6	20	0.8
Arthralgia	10	0.2	8	0
Metabolism and Nutrition				
Decreased appetite	15	0.9	10	0.8
Endocrine				
Hypothyroidism	11	0	1.5	0

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

Table 42: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-577

Laboratory Abnormality	Intravenous Nivolumab (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased AST	27	2.1	22	0.8
Increased alkaline phosphatase	25	0.8	18	0.8
Increased albumin	21	0.2	18	0
Increased ALT	20	1.9	16	1.2
Increased amylase	20	3.9	13	1.3
Hyponatremia	19	1.7	12	1.2
Hyperkalemia	17	0.8	15	1.6
Hypokalemia	12	1	11	1.2
Transaminases increased[b]	11	1.5	6	1.2
Hematology				
Lymphopenia	44	17	35	12
Anemia	27	0.8	21	0.4
Neutropenia	24	1.5	23	0.4

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

First-line Treatment of Unresectable Advanced or Metastatic ESCC

CHECKMATE-648

The safety of intravenous nivolumab in combination with chemotherapy or in combination with ipilimumab was evaluated in CHECKMATE-648, a randomized, active-controlled, multicenter, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC *[see Clinical Studies (14.11)]*. Patients received one of the following treatments:

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

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

Serious adverse reactions occurred in 62% of patients receiving intravenous nivolumab in combination with chemotherapy and in 69% of patients receiving intravenous nivolumab in combination with ipilimumab. The most frequent serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). The most frequent serious adverse reactions reported in ≥2% of patients who received intravenous nivolumab with ipilimumab were pneumonia (10%), pyrexia (4.3%), pneumonitis (4%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%).

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

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

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

Tables 43 and 44 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-648.

Table 43: Adverse Reactions in ≥10% of Patients - CHECKMATE-648

	Intravenous Nivolumab with	**Intravenous Nivolumab and**	**Cisplatin and 5-FU (n=304)**

Adverse Reaction	Cisplatin and 5-FU (n=310)		Ipilimumab (n=322)			
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal						
Nausea	65	4.2	22	0.6	56	2.6
Constipation	44	1.0	20	0.3	43	1
Stomatitis[a]	44	9	11	0.6	35	3
Diarrhea	29	2.9	22	1.9	20	2
Vomiting	23	2.3	15	1.6	19	3
Dysphagia	14	7	12	5	12	4.9
Abdominal pain[b]	13	1.9	10	0.9	11	0.7
Metabolism and Nutrition						
Decreased appetite	51	7	17	4	50	6
General						
Fatigue[c]	47	3.5	28	2.5	41	4.9
Pyrexia[d]	19	0.3	23	0.9	12	0.3
Edema[e]	16	0	7	0	13	0
Nervous System						
Peripheral neuropathy[f]	18	1.3	2.8	0	13	1
Psychiatric						
Insomnia	16	0	8	0	10	0.3
Skin and Subcutaneous Tissue						
Rash[g]	16	0.6	31	3.1	7	0
Pruritus	11	0	17	0.9	3.6	0
Alopecia	10	0			11	0
Respiratory, Thoracic and Mediastinal						
Cough[h]	16	0.3	13	0.3	13	0.3
Infections and Infestations						
Pneumonia[i]	13	5	14	8	10	2.6
Endocrine						
Hypothyroidism	7	0	14	0	0.3	0
Investigations						
Weight decreased	12	0.6	12	1.9	11	1
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[j]	11	0.3	14	0.6	8	0.3

Toxicity was graded per NCI CTCAE v4.

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

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

[c] Includes asthenia and malaise.

[d] Includes tumor associated fever.

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

[f] Includes hyperesthesia, hypoesthesia, peripheral motor neuropathy, peripheral

sensorimotor neuropathy, and peripheral sensory neuropathy.

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

[h] Includes productive cough.

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

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

Table 44: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-648

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

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

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

ATTRACTION-3

The safety of intravenous nivolumab was evaluated in ATTRACTION-3, a randomized, active-controlled, open-label, multicenter trial in 209 patients with unresectable advanced, recurrent or metastatic ESCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based chemotherapy *[see Clinical Studies (14.11)]*. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients received intravenous nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=209) or investigator's choice: docetaxel 75 mg/m^2 intravenously every 3 weeks (n=65) or paclitaxel 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off (n=143). Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 2.6 months (range: 0 to 29.2 months) in intravenous nivolumab-treated patients and 2.6 months (range: 0 to 21.4 months) in docetaxel- or paclitaxel-treated patients. Among patients who received intravenous nivolumab, 26% were exposed for >6 months and 10% were exposed for >1 year.

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

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

Tables 45 and 46 summarize the adverse reactions and laboratory abnormalities, respectively, in ATTRACTION-3.

Table 45: Adverse Reactions Occurring in ≥10% of Patients Receiving Intravenous Nivolumab - ATTRACTION-3

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

Infections				
Upper respiratory tract infection[e]	17	1	14	0
Pneumonia[f]	13	5	19	9
Respiratory, Thoracic and Mediastinal				
Cough[g]	16	0	14	0.5
General				
Pyrexia[h]	16	0.5	19	0.5
Fatigue[i]	12	1.4	27	4.8
Blood and Lymphatic System				
Anemia[j]	13	8	30	13
Endocrine				
Hypothyroidism[k]	11	0	1.4	0

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes hypophagia, and food aversion.

[c] Includes colitis.

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

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

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

[g] Includes productive cough.

[h] Includes tumor-associated fever.

[i] Includes asthenia.

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

[k] Includes blood thyroid stimulating hormone increased.

Table 46: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - ATTRACTION-3

Laboratory Abnormality	Intravenous Nivolumab (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatinine	78	0.5	68	0.5
Hyperglycemia	52	5	62	5
Hyponatremia	42	11	50	12
Increased AST	40	6	30	1
Increased alkaline	33	4.8	24	1.0

phosphatase				
Increased ALT	31	5	22	1.9
Hypercalcemia	22	6	14	2.9
Hyperkalemia	22	0.5	31	1
Hypoglycemia	14	1.4	14	0.5
Hypokalemia	11	2.9	13	3.4
Hematology				
Lymphopenia	46	19	72	43
Anemia	42	9	71	17
Leukopenia	11	0.5	79	45

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

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

CHECKMATE-649

The safety of intravenous nivolumab in combination with chemotherapy was evaluated in CHECKMATE-649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma *[see Clinical Studies (14.12)]*. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive or had untreated central nervous system (CNS) metastases. Patients were randomized to receive intravenous nivolumab in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

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

Patients were treated with intravenous nivolumab in combination with chemotherapy or chemotherapy until disease progression, unacceptable toxicity, or up to 2 years. The median duration of exposure was 6.8 months (range: 0 to 33.5 months) in intravenous nivolumab and chemotherapy-treated patients. Among patients who received intravenous nivolumab and chemotherapy, 54% were exposed for >6 months and 28% were exposed for >1 year.

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

The most frequent serious adverse reactions reported in ≥2% of patients treated with intravenous nivolumab in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). The most common adverse reactions reported in

≥20% of patients treated with intravenous nivolumab in combination with chemotherapy were peripheral neuropathy, nausea, fatigue, diarrhea, vomiting, decreased appetite, abdominal pain, constipation, and musculoskeletal pain.

Tables 47 and 48 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-649.

Table 47: Adverse Reactions in ≥10% of Patients Receiving Intravenous Nivolumab and Chemotherapy - CHECKMATE-649

Adverse Reaction	Intravenous Nivolumab and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	69	98	59
Nervous System				
Peripheral neuropathy[a]	53	7	46	4.8
Headache	11	0.8	6	0.3
Gastrointestinal				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain[b]	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis[c]	17	1.8	13	0.8
General				
Fatigue[d]	44	7	40	5
Pyrexia[e]	19	1	11	0.4
Edema[f]	12	0.5	8	0.1
Metabolism and Nutrition				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia[g]	14	0.3	9	0.3
Investigations				
Weight decreased	17	1.3	15	0.7
Increased lipase	14	7	8	3.7
Increased amylase	12	3.1	5	0.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[h]	20	1.3	14	2
Skin and Subcutaneous Tissue				
Rash[i]	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8
Respiratory, Thoracic and Mediastinal				
Cough[j]	13	0.1	9	0
Infections and Infestations				
Upper respiratory tract infection[k]	10	0.1	7	0.1

Toxicity was graded per NCI CTCAE v4.

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

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

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

[d] Includes asthenia.

[e] Includes tumor associated fever.

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

[g] Includes blood albumin decreased.

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

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, and rhinitis.

Table 48: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-649

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

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

6.2 Postmarketing Experience

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

Eye: Vogt-Koyanagi-Harada (VKH) syndrome

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

OPDIVO QVANTIG for subcutaneous injection contains nivolumab and hyaluronidase *[see Description (11)]*.

Nivolumab

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab intravenously twice weekly from the onset of organogenesis through delivery, at exposure levels of between 4 and 15 times higher than those observed at the clinical dose of 600 mg once every 2 weeks, 900 mg once every 3 weeks, or 1,200 mg once every 4 weeks (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to

nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response, and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Hyaluronidase

In an embryo-fetal development study, mice were dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is at least 6,600 times higher than the human dose of 10,000 U once every 2 weeks, 15,000 U once every 3 weeks, or 20,000 U once every 4 weeks (U/kg basis), when administered with nivolumab. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is at least 1,080 times higher than the human dose of 10,000 U once every 2 weeks, 15,000 U once every 3 weeks, or 20,000 U once every 4 weeks (U/kg basis), when administered with nivolumab.

8.2 Lactation

Risk Summary

There are no data on the presence of nivolumab or hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO QVANTIG.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

8.4 Pediatric Use

The safety and effectiveness of OPDIVO QVANTIG have been established in pediatric patients aged 12 years and older who weigh 30 kg or greater for the following indications:

- Unresectable or metastatic melanoma *[see Indications and Usage (1.2)]*
- Unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab *[see Indications and Usage (1.2)]*
- Completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma as adjuvant treatment *[see Indications and Usage (1.3)]*
- Unresectable or metastatic MSI-H or dMMR CRC following combination treatment with intravenous nivolumab and ipilimumab *[see Indications and Usage (1.9)]*
- MSI-H or dMMR mCRC that has progressed following treatment with a

fluoropyrimidine, oxaliplatin, irinotecan *[see Indications and Usage (1.9)]*

Use of OPDIVO QVANTIG in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies for intravenous nivolumab in adults and additional pharmacokinetic and safety data for intravenous nivolumab in pediatric patients 12 years and older who weigh 30 kg or greater *[see Adverse Reactions (6.1) and Clinical Studies (14)]*. Nivolumab exposure in pediatric patients 12 years and older who receive OPDIVO QVANTIG is predicted to be within range of those observed/predicted in adult patients at the recommended dosage *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*.

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

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

8.5 Geriatric Use

Monotherapy

Of the 248 patients who were randomized to monotherapy OPDIVO QVANTIG in clinical studies, 48% were 65 years and over and 14% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Single Agent Intravenous Nivolumab

Of 3569 patients with melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, ESCC, and esophageal or gastroesophageal junction cancer who were randomized to single agent intravenous nivolumab in clinical studies, 41% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients *[see Clinical Studies (14.1, 14.2, 14.3, 14.6, 14.8, 14.11, 14.12)]*.

Clinical studies in patients with recurrent head and neck SCC, or dMMR or MSI-H metastatic CRC (mCRC) who were treated with single agent intravenous nivolumab did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.7, 14.9)]*.

Intravenous Nivolumab in Combination with Platinum-Containing Chemotherapy

Of the 179 patients with NSCLC who were randomized to intravenous nivolumab in combination with platinum-doublet chemotherapy, 48% were 65 years old or older and 6% were 75 years old or older. No overall differences in safety or effectiveness were reported between patients older and younger than 65 years *[see Clinical Studies (14.4)]*.

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

Of the 1,110 patients with ESCC, GC, GEJC, or EAC who were randomized to intravenous nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy, 42% were 65 years or older and 10% were 75 years or older. No overall difference in

safety was reported between elderly patients and younger patients *[see Clinical Studies (14.11, 14.12)]*.

Of the 304 patients with UC who were treated with intravenous nivolumab in combination with gemcitabine and platinum-doublet chemotherapy, 40% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age and over and younger patients. Clinical studies of intravenous nivolumab with platinum-doublet chemotherapy did not include sufficient numbers of patients aged 75 years and over to determine whether safety and effectiveness differs compared to younger patients. *[see Clinical Studies (14.8)]*.

In Combination with Cabozantinib

Of the 320 patients with renal cell carcinoma who were treated with intravenous nivolumab in combination with cabozantinib, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients *[see Clinical Studies (14.1)]*.

11 DESCRIPTION

OPDIVO QVANTIG is a fixed-combination drug product containing nivolumab and hyaluronidase (human recombinant).

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

Hyaluronidase (human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Hyaluronidase (human recombinant) is a glycosylated single-chain protein produced by CHO cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (human recombinant) has a molecular weight of approximately 61 kDa.

OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) injection is a sterile, preservative-free, clear to opalescent, colorless to yellow solution that may contain a few translucent-to-white particles, supplied in a single-dose vial for subcutaneous use.

Each 2.5 mL single-dose vial contains 300 mg of nivolumab and 5,000 units of hyaluronidase (human recombinant), and the inactive ingredients: histidine (3.88 mg), histidine hydrochloride monohydrate (5.25 mg), methionine (1.87 mg), pentetic acid (0.049 mg), polysorbate 80 (1.25 mg), sucrose (214 mg), and Water for Injection, USP. The pH is 5.5 to 6.5.

Each 5 mL single-dose vial contains 600 mg of nivolumab and 10,000 units of hyaluronidase (human recombinant), and the inactive ingredients: histidine (7.75 mg), histidine hydrochloride monohydrate (10.5 mg), methionine (3.73 mg), pentetic acid (0.0985 mg), polysorbate 80 (2.5 mg), sucrose (428 mg), and Water for Injection, USP. The pH is 5.5 to 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. 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 temporarily depolymerizing hyaluronan. In the doses administered, hyaluronidase in OPDIVO QVANTIG acts transiently and locally. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

12.2 Pharmacodynamics

Exposure-Response Relationship

The exposure-response relationship and time course of pharmacodynamics of OPDIVO QVANTIG have not been fully characterized.

12.3 Pharmacokinetics

Nivolumab 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 geometric mean (CV%) unless otherwise specified.

When comparing nivolumab exposures following OPDIVO QVANTIG to those of intravenous nivolumab in CHECKMATE-67T *[see Clinical Studies (14.1)]*, the geometric mean ratios (GMRs) (90% CI) for time-averaged concentration (C_{avg}) over 28 days and at steady state were 2.10 (2.00, 2.20) and 1.98 (1.87, 2.11), respectively, and for minimum concentration (C_{min}) at 28 days and at steady state were 1.60 (1.49, 1.72) and 1.77 (1.63, 1.93), respectively.

Nivolumab steady state was achieved by 16 weeks. The systemic accumulation ratio was 2.3.

Absorption

Nivolumab bioavailability is 74% (14%). Peak concentrations occurred by approximately 6 days.

Distribution

The volume of distribution at steady state is 6.8 L (27%).

Elimination

Nivolumab clearance decreases over time, with a maximal reduction from baseline values of 24.5% (47.6%), resulting in a steady-state clearance of 8.2 mL/h (53.9%) in patients with metastatic tumors; this decrease in clearance is not considered clinically relevant.

Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state.

The elimination half-life is 25 days (78%).

Specific Populations

No clinically significant differences in the pharmacokinetics of nivolumab were observed based on body weight (35 to 153 kg), sex, eGFR (24 to 124 mL/min/1.73 m^2), and performance status.

Pediatric Patients

Nivolumab exposures in pediatric patients 12 years and older who weigh 30 kg or greater are predicted to be within range of those observed in adults at the recommended dosage *[see Dosage and Administration (2.3)]*.

12.6 Immunogenicity

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

During the 2-year treatment period in CHECKMATE-67T *[see Clinical Studies (14.1)]*, 23% (46/202) of patients who received OPDIVO QVANTIG developed anti-nivolumab antibodies (ADA) and 4.3% (2/46) had neutralizing antibodies against nivolumab (NAb). The corresponding incidence of ADA was 7% (15/215) and NAb was 0% (0/15) for intravenous nivolumab in the same study. The incidence of anti-hyaluronidase antibodies in CHECKMATE-67T was 8.8% (19/215); 5 (26%) of these 19 patients developed NAb.

Nivolumab clearance increased by approximately 26% in patients who received OPDIVO QVANTIG and tested positive for ADA compared to patients who tested negative for ADA; this change in clearance is not considered clinically significant. Local injection-site reactions were reported in 15% (7/46) of patients who developed ADA to nivolumab and 7% (10/155) of patients who did not develop ADA to nivolumab; however, all events were Grade 1 or 2 and resolved. Because of low occurrence of anti-nivolumab or anti-hyaluronidase antibodies, the effect of ADA on the effectiveness of OPDIVO QVANTIG is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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 hyaluronidase.

In addition, when subcutaneous hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is at least 600 times higher than the human dose (U/kg basis), of 10,000 U once every 2 weeks, 15,000 U once every 3 weeks, or 20,000 U once every 4 weeks, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *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 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma - OPDIVO QVANTIG

The efficacy of OPDIVO QVANTIG was evaluated in CHECKMATE-67T (NCT04810078), a multicenter, randomized, open-label study in patients with advanced or metastatic clear cell renal cell carcinoma. Patients 18 years of age or older with histologically confirmed advanced or metastatic renal cell carcinoma with a clear cell component, including those with sarcomatoid features, and who received no more than 2 prior systemic treatment regimens were randomized to receive OPDIVO QVANTIG (containing 1,200 mg of nivolumab and 20,000 units of hyaluronidase) every 4 weeks subcutaneously, or nivolumab 3 mg/kg every 2 weeks intravenously. Patients with untreated, symptomatic central nervous system (CNS) metastases; leptomeningeal metastases; concurrent malignancies requiring treatment or history of prior malignancy within the previous 2 years; active, known, or suspected autoimmune disease; or who received prior treatment with a checkpoint inhibitor were excluded from the study. Patients with asymptomatic, stable CNS metastases that did not require immediate treatment were eligible if there was no evidence of progression within 28 days prior to the first dose of study drug administration. Stratification factors for randomization were weight (<80 kg vs ≥80 kg) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification (favorable vs intermediate, vs poor risk). The primary objective was to assess the nivolumab exposure of subcutaneous administration of OPDIVO QVANTIG as compared to the intravenous administration of nivolumab. The secondary objective of the study was to evaluate overall response rate (ORR) by blinded independent central review (BICR).

A total of 495 patients were randomized to receive either OPDIVO QVANTIG (n=248) or intravenous nivolumab (n=247). The median age was 65 years (range: 20 to 93), with 51% ≥65 years of age and 14% ≥75 years of age; 68% male; 85% White, 12.5% not reported, 1% American Indian or Alaska Native, 0.8% Asian, and 0.4% Black; 36% Hispanic or Latino, 33% not Hispanic or Latino, and 31% not reported. Fifty-seven percent of patients weighed <80 kg and 43% weighed ≥80 kg. Baseline Karnofsky

performance status was 70 (7%), 80 (20%), 90 (34%), or 100 (39%). Patient distribution by IMDC risk categories was 21% favorable, 62% intermediate, and 17% poor.

When comparing subcutaneous administration of OPDIVO QVANTIG to the intravenous administration of nivolumab, CHECKMATE-67T met the predefined acceptance margin for pharmacokinetic endpoints, with the lower boundary of 90% confidence interval of geometric mean ratios of not less than 0.8 for both serum nivolumab C_{avg} over 28 days and C_{min} at steady state. *[see Clinical Pharmacology 12.3].* Efficacy results are shown in Table 49.

Table 49: Efficacy Results - CHECKMATE-67T

	OPDIVO QVANTIG N=248	**Intravenous Nivolumab N=247**
ORR per BICR, n (%)	60 (24)	45 (18)
95% CI[a]	(19, 30)	(14, 24)

[a] Confidence interval based on the Clopper and Pearson method.

RCC Trials - Intravenous Nivolumab

The effectiveness of OPDIVO QVANTIG has been established for the following:

- as monotherapy, for advanced renal cell carcinoma (RCC) following treatment with intravenous nivolumab and ipilimumab combination therapy (CHECKMATE-214 study).
- in combination with cabozantinib, for the first-line treatment of adult patients with advanced RCC (CHECKMATE-9ER study).
- as monotherapy, for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy (CHECKMATE-025 study).

Use of OPDIVO QVANTIG for these RCC indications is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab in the CHECKMATE-67T trial *[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 nivolumab in these RCC populations.

First-line Renal Cell Carcinoma

CHECKMATE-214

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label trial in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of >10 mg/dL, platelet

count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to nivolumab 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg intravenously every two weeks (n=425), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=422). Treatment continued until disease progression or unacceptable toxicity.

The trial population characteristics were: median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to intravenous nivolumab and ipilimumab as compared with sunitinib (Table 50 and Figure 1). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. Efficacy results are shown in Table 50 and Figure 1.

Table 50: Efficacy Results - CHECKMATE-214

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

[a] Not Reached

[b] Based on a stratified proportional hazards model.

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

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

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

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

[g] Not Significant at alpha level of 0.009.

Figure 1: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to intravenous nivolumab and ipilimumab (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving intravenous nivolumab and ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of intravenous nivolumab and ipilimumab in previously untreated renal cell carcinoma with favorable-risk disease has not been established.

CHECKMATE-9ER

CHECKMATE-9ER (NCT03141177) was a randomized, open-label study of intravenous nivolumab combined with cabozantinib versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression (≥1% vs. <1% or indeterminate), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World).

Patients were randomized to nivolumab 240 mg intravenously every 2 weeks and cabozantinib 40 mg orally daily (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328).

Treatment continued until disease progression per RECIST v1.1 or unacceptable toxicity. Treatment beyond RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 28 to 90) with 38% ≥65 years of age and 10% ≥75 years of age. The majority of patients were male (74%) and White (82%) and 23% and 77% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. Patient distribution by IMDC risk categories was 22% favorable, 58% intermediate, and 20% poor.

The major efficacy outcome measure was PFS (BICR assessed). Additional efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to intravenous nivolumab and cabozantinib compared with sunitinib. Consistent results for PFS were observed across pre-specified subgroups of IMDC risk categories and PD-L1 tumor expression status. An updated OS analysis was conducted when 271 deaths were observed based on the pre-specified number of deaths for the pre-planned final analysis of OS. Efficacy results are shown in Table 51 and Figures 2 and 3.

Table 51: Efficacy Results - CHECKMATE-9ER

	Intravenous Nivolumab and Cabozantinib (n=323)	**Sunitinib (n=328)**
Progression-free Survival		
Disease progression or death (%)	144 (45)	191 (58)
Median PFS (months)[a] (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI)[b]	0.51 (0.41, 0.64)	
p-value[c,d]	<0.0001	
Overall Survival		
Deaths (%)	67 (21)	99 (30)
Median OS (months)[a] (95% CI)	NR[e]	NR (22.6, NR[e])
Hazard ratio (98.89% CI)[b]	0.60 (0.40, 0.89)	
p-value[c,d,f]	0.0010	
Updated Overall Survival		
Deaths (%)	121 (37)	150 (46)
Median OS (months)[a] (95% CI)	37.7 (35.5, NR)	34.3 (29.0, NR)
Hazard ratio (95% CI)[b]	0.70 (0.55, 0.90)	
Confirmed Objective Response Rate (95% CI)[g]	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value[h]	<0.0001	
Complete Response	26 (8%)	15 (4.6%)
Partial Response	154 (48%)	74 (23%)
Median duration of response in months (95% CI)[a]	20.2 (17.3, NR[e])	11.5 (8.3, 18.4)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model.

[c] Based on stratified log-rank test

[d] 2-sided p-values from stratified log-rank test.
[e] Not Reached
[f] p-value is compared with the allocated alpha of 0.0111 for this interim analysis
[g] CI based on the Clopper-Pearson method.
[h] 2-sided p-value from Cochran-Mantel-Haenszel test.

Figure 2: Progression-free Survival - CHECKMATE-9ER

Figure 3: Updated Overall Survival - CHECKMATE-9ER

In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR (95% CI) of 1.03 (0.55, 1.92), 0.74 (0.54, 1.01), 0.65 (0.50, 0.85), and 0.49 (0.31, 0.79), respectively.

Previously Treated Renal Cell Carcinoma

CHECKMATE-025

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label trial in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. The trial excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies. Patients were randomized to nivolumab 3 mg/kg by intravenous infusion every 2 weeks (n=410) or everolimus 10 mg orally daily (n=411). The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. The major efficacy outcome measure was overall survival (OS).

The trial population characteristics were: median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and White (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were

treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The trial demonstrated a statistically significant improvement in OS for patients randomized to intravenous nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis). OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 52 and Figure 4.

Table 52: Efficacy Results - CHECKMATE-025

	Intravenous Nivolumab (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival (months) (95% CI)	25.0 (21.7, NR[a])	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[b]	0.73 (0.60, 0.89)	
p-value[c,d]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response (months) (95% CI)	23.0 (12.0, NR[a])	13.7 (8.3, 21.9)
Median time to onset of confirmed response (months) (min, max)	3.0 (1.4, 13.0)	3.7 (1.5, 11.2)

[a] Not Reached

[b] Based on a stratified proportional hazards model.

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

[d] p-value is compared with 0.0148 of the allocated alpha for this interim analysis.

Figure 4: Overall Survival - CHECKMATE-025

14.2 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The effectiveness of OPDIVO QVANTIG has been established for the treatment of previously treated unresectable or metastatic melanoma in adult and pediatric patients 12 years and older who weigh 30 kg or greater. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of this adequate and well-controlled study of intravenous nivolumab in this melanoma population.

CHECKMATE-037

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

9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

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

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

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

There were responses in patients with and without BRAF V600 mutation-positive melanoma. A total of 405 patients were randomized and the median duration of OS was 15.7 months (95% CI: 12.9, 19.9) in nivolumab-treated patients compared to 14.4 months (95% CI: 11.7, 18.2) (HR 0.95; 95.54% CI: 0.73, 1.24) in patients assigned to investigator’s choice of treatment. Figure 5 summarizes the OS results.

Figure 5: Overall Survival - CHECKMATE-037*

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

Previously Untreated Metastatic Melanoma

The effectiveness of OPDIVO QVANTIG has been established for the treatment of previously untreated unresectable or metastatic melanoma in adult and pediatric patients 12 years and older who weigh 30 kg or greater. Use of OPDIVO QVANTIG for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of these adequate and well-controlled studies of intravenous nivolumab in this melanoma population.

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either nivolumab 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or

acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and ORR per RECIST v1.1.

The trial population characteristics were: median age was 65 years (range: 18 to 87), 59% were male, and 99.5% were White. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 ≥5% tumor cell membrane expression (35%), and history of brain metastasis (4%). More patients in the intravenous nivolumab arm had an ECOG performance status of 0 (71% vs. 58%).

CHECKMATE-066 demonstrated a statistically significant improvement in OS for the intravenous nivolumab arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of intravenous nivolumab-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 53 and Figure 6.

Table 53: Efficacy Results - CHECKMATE-066

	Intravenous Nivolumab (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median (months) (95% CI)	NR[a]	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[b]	0.42 (0.30, 0.60)	
p-value[c,d]	<0.0001	
Progression-free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median (months) (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI)[b]	0.43 (0.34, 0.56)	
p-value[c,d]	<0.0001	
Overall Response Rate	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

[a] Not Reached.

[b] Based on a stratified proportional hazards model.

[c] Based on stratified log-rank test.

[d] p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

Figure 6: Overall Survival - CHECKMATE-066

CHECKMATE-067

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in 945 patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: intravenous nivolumab and ipilimumab, intravenous nivolumab, or ipilimumab. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

- Intravenous nivolumab 1 mg/kg with ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (nivolumab and ipilimumab arm),
- Nivolumab 3 mg/kg by intravenous infusion every 2 weeks (nivolumab arm), or
- Ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks (ipilimumab arm).

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the AJCC staging system (M0, M1a, M1b vs. M1c). Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The major efficacy outcome measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either intravenous nivolumab-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to intravenous nivolumab improves PFS or OS compared to intravenous nivolumab as a single agent. Efficacy results are shown in Table 54 and Figure 7.

Table 54: Efficacy Results - CHECKMATE-067

	Intravenous Nivolumab and Ipilimumab (n=314)	**Intravenous Nivolumab (n=316)**	**Ipilimumab (n=315)**
Overall Survival[a]			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.55 (0.44, 0.69)	0.63 (0.50, 0.78)	
p-value[c, d]	<0.0001	<0.0001	
Progression-free Survival[a]			
Disease progression or death	151 (48%)	174 (55%)	234 (74%)
Median (months) (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.42 (0.34, 0.51)	0.57 (0.47, 0.69)	
p-value[c, e]	<0.0001	<0.0001	
Confirmed Overall Response Rate[a]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[f]	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
Duration of Response			
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

[a] OS results are based on final OS analysis with 28 months of minimum follow-up; PFS (co-primary endpoint) and ORR (secondary endpoint) results were based on primary analysis with 9 months of minimum follow-up.

[b] Based on a stratified proportional hazards model.

[c] Based on stratified log-rank test.

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

[e] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.

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

+ Censored observation

Figure 7: Overall Survival - CHECKMATE-067

Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the intravenous nivolumab and ipilimumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the intravenous nivolumab arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the intravenous nivolumab and ipilimumab arm, 6.9 months (95% CI: 4.3, 9.5) in the intravenous nivolumab arm, and 2.9 months (95% CI: 2.8, 3.2) in the ipilimumab arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥24 months was 55% in the intravenous nivolumab and ipilimumab arm, 56% in the intravenous nivolumab arm, and 39% in the ipilimumab arm.

14.3 Adjuvant Treatment of Melanoma

The effectiveness of OPDIVO QVANTIG has been established for the adjuvant treatment of Stage IIB, Stage IIC, Stage III, or Stage IV melanoma in adult and pediatric patients 12 years and older who weigh 30 kg or greater. Use of OPDIVO QVANTIG for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of these adequate and well-controlled

studies of intravenous nivolumab in these melanoma populations.

CHECKMATE-76K

CHECKMATE-76K (NCT04099251) was a randomized, double-blind trial in 790 patients with completely resected Stage IIB/C melanoma. Patients were randomized (2:1) to receive nivolumab 480 mg or placebo by intravenous infusion every 4 weeks for up to 1 year or until disease recurrence or unacceptable toxicity. Enrollment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node within 12 weeks prior to randomization, and ECOG performance status of 0 or 1. The trial excluded patients with ocular/uveal or mucosal melanoma, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery. Randomization was stratified by AJCC 8^{th} staging system edition (T3b vs. T4a vs. T4b). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurred first and as assessed by the investigator. Tumor assessments were conducted every 26 weeks during years 1-3 and every 52 weeks thereafter until year 5.

The trial population characteristics were: median age 62 years (range: 19 to 92), 61% were male, 98% were White, 0.4% Black or African American, 0.1% Asian, and 1.1% race unknown, 2.2% Hispanic or Latino, 58% Not Hispanic or Latino, 40% ethnicity unknown, and 94% had an ECOG performance status of 0. Sixty one percent had stage IIB and 39% had stage IIC melanoma.

CHECKMATE-76K demonstrated a statistically significant improvement in RFS for patients randomized to the intravenous nivolumab arm compared with the placebo arm. Efficacy results are shown in Table 55 and Figure 8.

Table 55: Efficacy Results - CHECKMATE-76K

	Intravenous Nivolumab n=526	**Placebo n=264**
Recurrence-free Survival		
Number of events, n (%)	66 (13%)	69 (26%)
Median (months)[b] (95% CI)	NR[a] (28.5, NR)	NR[a] (21.6, NR)
Hazard ratio[c] (95% CI) p-value[d]	0.42 (0.30, 0.59) p<0.0001	

[a] Not reached.

[b] Based on Kaplan-Meier estimates.

[c] Hazard Ratio is intravenous nivolumab over placebo based on a stratified Cox proportional hazard model.

[d] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value <0.033.

Figure 8: Recurrence-free Survival - CHECKMATE-76K

CHECKMATE-238

CHECKMATE-238 (NCT02388906) was a randomized, double-blind trial in 906 patients with completely resected Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive nivolumab 3 mg/kg by intravenous infusion every 2 weeks or ipilimumab 10 mg/kg intravenously every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior to randomization. The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs. negative/indeterminate) and AJCC stage (Stage IIIB/C vs. Stage IV M1a-M1b vs. Stage IV M1c). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurs first and as assessed by the investigator. Patients underwent imaging for tumor recurrence every 12 weeks for the first 2 years then every 6 months thereafter.

The trial population characteristics were: median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients

randomized to the intravenous nivolumab arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 56 and Figure 9.

Table 56: Efficacy Results - CHECKMATE-238

	Intravenous Nivolumab N=453	**Ipilimumab 10 mg/kg N=453**
Recurrence-free Survival		
Number of events, n (%)	154 (34%)	206 (45%)
Median (months) (95% CI)	NR[a]	NR[a] (16.56, NR[a])
Hazard ratio[b] (95% CI) p-value[c,d]	0.65 (0.53, 0.80) p<0.0001	
Overall Survival		
Number of events, n (%)[e]	100 (22%)	111 (25%)
Median (months) (95% CI)	NR[a]	NR[a]
Hazard ratio[b] (95% CI) p-value	0.87 (0.67, 1.14) 0.3148	

[a] Not reached.

[b] Based on a stratified proportional hazards model.

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

[d] p-value is compared with 0.0244 of the allocated alpha for this analysis.

[e] At the time of the final OS analysis, fewer overall survival events were observed than originally anticipated (approximately 302).

Figure 9: Recurrence-free Survival - CHECKMATE-238

14.4 Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

The effectiveness of OPDIVO QVANTIG has been established for the neoadjuvant treatment of resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum doublet chemotherapy. Use of OPDIVO QVANTIG for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab (CHECKMATE-816, NCT02998528), and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this lung cancer population.

CHECKMATE-816

CHECKMATE-816 (NCT02998528) was a randomized, open label trial in patients with resectable NSCLC. The trial included patients with resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA NSCLC (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria), ECOG performance status 0 or 1, and measurable disease (per RECIST version 1.1). Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients were randomized to receive either:

- nivolumab 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered intravenously every 3 weeks for up to 3

cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-doublet chemotherapy consisted of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology). In the platinum-doublet chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology).

Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). Tumor assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The major efficacy outcome measures were event-free survival (EFS) based on blinded independent central review (BICR) assessment and pathologic complete response (pCR) as evaluated by blinded independent pathology review (BIPR). Additional efficacy outcome measures included OS.

A total of 358 patients were randomized to receive either intravenous nivolumab in combination with platinum-doublet chemotherapy (n=179) or platinum-doublet chemotherapy (n=179). The median age was 65 years (range: 34 to 84) with 51% of patients ≥65 years and 7% of patients ≥75 years, 50% were Asian, 47% were White, 2% were Black, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% had tumors with PD-L1 expression ≥1%; 35% had stage IB/II and 64% had stage IIIA disease; 51% had tumors with squamous histology and 49% had tumors with non-squamous histology; and 89% were former/current smokers.

Eighty-three percent of patients in the intravenous nivolumab in combination with platinum-doublet chemotherapy arm had definitive surgery compared to 75% of patients in the platinum-doublet chemotherapy arm.

The study demonstrated statistically significant improvements in EFS and pCR. Efficacy results are presented in Table 57 and Figure 10.

Table 57: Efficacy Results - CHECKMATE-816

	Intravenous Nivolumab and Platinum-Doublet Chemotherapy (n=179)	**Platinum-Doublet Chemotherapy (n=179)**
Event-free Survival (EFS) per BICR		
Events (%)	64 (35.8)	87 (48.6)
Median (months) [a] (95% CI)	31.6 (30.2, NR)	20.8 (14.0, 26.7)
Hazard Ratio[b] (95% CI)	0.63 (0.45, 0.87)	
Stratified log-rank p-value[c]	0.0052	
Pathologic Complete Response (pCR) per BIPR		
Number of patients with pCR	43	4
pCR Rate (%), (95% CI)[d]	24.0 (18.0, 31.0)	2.2 (0.6, 5.6)

Estimated treatment difference (95% CI)[e]	21.6 (15.1, 28.2)
p-value[f]	<0.0001

Minimum follow-up for EFS was 21 months.

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.

[d] Based on Clopper and Pearson method.

[e] Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

[f] From stratified CMH test.

Figure 10: Event-Free Survival - CHECKMATE-816

At the time of the EFS analysis, 26% of the patients had died. A prespecified interim analysis for OS resulted in a HR of 0.57 (95% CI: 0.38, 0.87), which did not cross the boundary for statistical significance.

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

The effectiveness of OPDIVO QVANTIG has been established for neoadjuvant treatment of resectable (tumors ≥4 cm or node positive) NSCLC and no EGFR mutations or ALK

rearrangements in combination with platinum doublet chemotherapy followed by adjuvant treatment with intravenous nivolumab. Use of OPDIVO QVANTIG for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab (CHECKMATE-77T, NCT04025879), and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this lung cancer population.

CHECKMATE-77T

The efficacy of intravenous nivolumab, in combination with platinum-doublet chemotherapy, followed by surgery, and continued adjuvant treatment with intravenous nivolumab as a single agent, was investigated in CHECKMATE-77T (NCT04025879), a randomized, double-blind trial in 461 patients with resectable NSCLC. The trial included patients with resectable, suspected or histologically confirmed Stage IIA (>4 cm) to IIIB (T3-T4 N2) NSCLC (per the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual), and ECOG performance status 0 or 1. Patients with unresectable or metastatic NSCLC, EGFR mutations or known ALK translocations, brain metastasis, Grade 2 or greater peripheral neuropathy, interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomization was stratified by tumor PD-L1 expression level (≥1% versus <1% versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumor histology (squamous versus nonsquamous).

Patients were randomized (1:1) to receive either:

- Neoadjuvant nivolumab 360 mg administered intravenously over 30 minutes in combination with one of the following platinum-doublet chemotherapy regimens every 3 weeks for four cycles:
    - Paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology)
    - Pemetrexed 500 mg/m2, and cisplatin 75 mg/m^2 or carboplatin AUC 5 or AUC 6 (nonsquamous histology)
    - Cisplatin 75 mg/m^2 and docetaxel 75 mg/m2 (squamous histology).

  Within 90 days after the surgery, nivolumab 480 mg was administered intravenously over 30 minutes every 4 weeks.

or

- Neoadjuvant placebo administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy *(see above)* every 3 weeks for four cycles. Within 90 days after the surgery, placebo was administered intravenously over 30 minutes every 4 weeks.

All study medications were administered via intravenous infusion. Treatment continued until disease progression, recurrence, or unacceptable toxicity for up to 13 cycles (1 year). Tumor assessments were performed every 12 weeks for 2 years, then every 24 weeks for up to 5 years or until disease recurrence or progression was confirmed by BICR.

The trial was not designed to isolate the effect of intravenous nivolumab in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included overall survival (OS), pathologic complete response (pCR), and major pathologic response (MPR).

The median age was 66 years (range: 35 to 86); 71% were male; 72% were White, 25% were Asian, 1.7% were Black, and 1.5% were mixed race/ race unknown/ not reported; and 6% were Hispanic or Latino. Baseline ECOG performance status was 0 (62%) or 1 (38%); 56% had tumors with PD-L1 expression ≥1% and 40% had tumors with PD-L1 expression <1%; 35% had stage II and 64% had stage III disease; 23% had N1 disease and 39% had N2 disease; 51% had tumors with squamous histology and 49% had tumors with nonsquamous histology; and 90% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant intravenous nivolumab in combination with platinum-doublet chemotherapy followed by adjuvant intravenous nivolumab arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm.

The study demonstrated a statistically significant improvement in EFS for patients treated with neoadjuvant intravenous nivolumab in combination with platinum-doublet chemotherapy followed by single agent intravenous nivolumab compared with patients randomized to placebo in combination with platinum-doublet chemotherapy followed by placebo. Efficacy results are presented in Table 58 and Figure 11.

Table 58: Efficacy Results - CHECKMATE-77T

	Neoadjuvant Intravenous Nivolumab and Platinum-Doublet Chemotherapy/Adjuvant Intravenous Nivolumab (n=229)	**Neoadjuvant Placebo and Platinum-Doublet Chemotherapy/Adjuvant Placebo (n=232)**
Event-free Survival (EFS) per BICR		
Events (%)	76 (33%)	113 (49%)
Median (months)[a] (95% CI)	NR (28.9, NR)	18.4 (13.6, 28.1)
Hazard Ratio[b] (95% CI)	0.58 (0.43, 0.78)	
Stratified log-rank p-value[c]	0.00025	

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0264.

Figure 11: Event-Free Survival - CHECKMATE-77T

In a pre-specified descriptive analysis, the pCR rate was 25% (95% CI: 20, 31) in the intravenous nivolumab arm and 4.7% (95% CI: 2.4, 8) in the placebo arm.

At the time of the EFS analysis, OS data were immature.

14.6 Metastatic Non-Small Cell Lung Cancer

Second-line Treatment of Metastatic NSCLC

The effectiveness of OPDIVO QVANTIG has been established for the treatment of NSCLC previously treated with platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG. Use of OPDIVO QVANTIG for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of this adequate and well-controlled study of intravenous nivolumab in this lung cancer population.

CHECKMATE-017

CHECKMATE-017 (NCT01642004) was a randomized (1:1), open-label trial in 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks (n=135) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=137). Randomization was stratified

by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This trial included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS.

The trial population characteristics were: median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were White (93%) and male (76%); the majority of patients were enrolled in Europe (57%) with the remainder in US/Canada (32%) and the rest of the world (11%). Baseline ECOG performance status was 0 (24%) or 1 (76%) and 92% were former/current smokers. Baseline disease characteristics of the population as reported by investigators were Stage IIIb (19%), Stage IV (80%), and brain metastases (6%). All patients received prior therapy with a platinum-doublet regimen and 99% of patients had tumors of squamous-cell histology.

The trial demonstrated a statistically significant improvement in OS for patients randomized to intravenous nivolumab as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Efficacy results are shown in Table 59 and Figure 12.

Table 59: Efficacy Results - CHECKMATE-017

	Intravenous Nivolumab (n=135)	**Docetaxel (n=137)**
Overall Survival		
Deaths (%)	86 (64%)	113 (82%)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Hazard ratio (95% CI)[a]	0.59 (0.44, 0.79)	
p-value[b,c]	0.0002	
Overall Response Rate	27 (20%)	12 (9%)
(95% CI)	(14, 28)	(5, 15)
p-value[d]	0.0083	
Complete response	1 (0.7%)	0
Median duration of response (months) (95% CI)	NR[e] (9.8, NR[e])	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with 0.0315 of the allocated alpha for this interim analysis.
[d] Based on the stratified Cochran-Mantel-Haenszel test.
[e] Not Reached

Figure 12: Overall Survival - CHECKMATE-017

Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the trial population, 17% of 272 patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1 and 53% had PD-L1 positive squamous NSCLC defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive subgroup.

CHECKMATE-057

CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks (n=292) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=290). Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung

disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (92%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%).

CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to intravenous nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 60 and Figure 13.

Table 60: Efficacy Results - CHECKMATE-057

	Intravenous Nivolumab (n=292)	**Docetaxel (n=290)**
Overall Survival		
Deaths (%)	190 (65%)	223 (77%)
Median (months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.0, 10.7)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0015	
Overall Response Rate	56 (19%)	36 (12%)
(95% CI)	(15, 24)	(9, 17)
p-value[d]	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Median duration of response (months) (95% CI)	17 (8.4, NR[e])	6 (4.4, 7.0)
Progression-free Survival		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI)[a]	0.92 (0.77, 1.11)	
p-value[b]	0.39	

[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with .0408 of the allocated alpha for this interim analysis.

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

[e] Not Reached.

Figure 13: Overall Survival - CHECKMATE-057

Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the trial population, 22% of 582 patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% had ≥1% but <5% tumor cells with positive staining, 7% had ≥5% but <10% tumor cells with positive staining, and 67% had ≥10% tumor cells with positive staining. Figures 14 and 15 summarize the results of prespecified analyses of OS and PFS in subgroups determined by percentage of tumor cells expressing PD-L1.

Figure 14: Forest Plot: OS Based on PD-L1 Expression - CHECKMATE-057

Figure 15: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057

14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

The effectiveness of OPDIVO QVANTIG has been established for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this head and neck carcinoma population.

CHECKMATE-141

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label

trial enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive nivolumab 3 mg/kg by intravenous infusion every 2 weeks or investigator's choice of cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously weekly).

Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR.

A total of 361 patients were randomized; 240 patients to the intravenous nivolumab arm and 121 patients to the investigator's choice arm (docetaxel: 45%; methotrexate: 43%; and cetuximab: 12%). The trial population characteristics were: median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male. Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 45% of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy, and 25% had HPVp16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status.

The trial demonstrated a statistically significant improvement in OS for patients randomized to intravenous nivolumab as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs. 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively). Efficacy results are shown in Table 61 and Figure 16.

Table 61: Overall Survival - CHECKMATE-141

	Intravenous Nivolumab (n=240)	**Cetuximab, Methotrexate or Docetaxel (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[a] Based on stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with 0.0227 of the allocated alpha for this interim analysis.

Figure 16: Overall Survival - CHECKMATE-141

Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the trial population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup.

14.8 Urothelial Carcinoma

Adjuvant Treatment of Urothelial Carcinoma (UC) at High Risk of Recurrence

The effectiveness of OPDIVO QVANTIG has been established for the adjuvant treatment of UC at high risk of recurrence. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO

QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this UC population.

CHECKMATE-274

CHECKMATE-274 (NCT02632409) was a randomized, double-blind, placebo-controlled study of adjuvant intravenous nivolumab in patients who were within 120 days of radical resection (R0) of UC of the bladder or upper urinary tract (renal pelvis or ureter) at high risk of recurrence. High risk of recurrence was defined as either 1) ypT2-ypT4a or ypN^+ for patients who received neoadjuvant cisplatin or 2) pT3-pT4a or pN^+ for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin. Patients were randomized 1:1 to receive nivolumab 240 mg or placebo by intravenous infusion every 2 weeks until recurrence or until unacceptable toxicity for a maximum treatment duration of 1 year. Patients were stratified by pathologic nodal status (N+ vs. N0/x with <10 nodes removed vs. N0 with ≥10 nodes removed), tumor cells expressing PD-L1 (≥1% vs. <1%/indeterminate as determined by the central lab using the PD-L1 IHC 28-8 pharmDx assay), and use of neoadjuvant cisplatin (yes vs. no).

The trial population characteristics were: median age of 67 years (range: 30 to 92); 76% male; 76% White, 22% Asian, 0.7% Black, and 0.1% American Indian or Alaska Native. Of the 335 (47%) of patients with node-positive UC, 44 (6%) had non–muscle-invasive (<pT2) primary tumors. ECOG performance status was 0 (63%), 1 (35%), or 2 (2%). Prior neoadjuvant cisplatin had been given to 43% of patients; of the 57% who did not receive prior neoadjuvant cisplatin, reasons listed were ineligibility (22%), patient preference (33%), and other/not reported (2%). Tumor PD-L1 expression was ≥1% in 40% of patients, and 21% of patients had upper tract UC.

The major efficacy outcome measures were investigator-assessed DFS in all randomized patients and in patients with tumors expressing PD-L1 ≥1%. DFS was defined as time to first recurrence (local urothelial tract, local non-urothelial tract, or distant metastasis), or death. Additional efficacy outcome measures included OS.

At the pre-specified interim analysis, CHECKMATE-274 demonstrated a statistically significant improvement in DFS for patients randomized to intravenous nivolumab vs. placebo in the all randomized patient population, as well as in the subpopulation of patients with PD-L1 ≥1%, as shown in Table 62 and Figure 17.

In exploratory subgroup analyses in patients with upper tract UC (n=149), no improvement in DFS was observed in the nivolumab arm compared to the placebo arm. The unstratified DFS hazard ratio estimate was 1.15 (95% CI: 0.74, 1.80).

In an exploratory subgroup analysis in patients with PD-L1 expression of <1% (n=414), the unstratified DFS hazard ratio estimate was 0.83 (95% CI: 0.64, 1.08).

OS data is immature with 33% of deaths in the overall randomized population. In the UTUC subpopulation, 37 deaths occurred (20 in the nivolumab arm, 17 in the placebo arm).

Table 62: Efficacy Results - CHECKMATE-274

	All Randomized		**PD-L1 ≥1%**	
	Intravenous Nivolumab (n=353)	**Placebo (n=356)**	**Intravenous Nivolumab (n=140)**	**Placebo (n=142)**

Disease-free Survival				
Events[a], n (%) Local recurrence Distant recurrence Death	170 (48) 47 (13) 108 (31) 14 (4)	204 (57) 64 (18) 127 (36) 10 (3)	55 (39) 10 (7) 40 (29) 5 (4)	81 (57) 24 (17) 52 (37) 5 (4)
Median DFS (months)[b] (95% CI)	20.8 (16.5, 27.6)	10.8 (8.3, 13.9)	N.R. (21.2, N.E.)	8.4 (5.6, 21.2)
Hazard ratio[c] (95% CI)	0.70 (0.57, 0.86)		0.55 (0.39, 0.77)	
p-value	0.0008[d]		0.0005[e]	

N.R. Not Reached, N.E. Not Estimable

[a] Includes disease at baseline events (protocol deviations): n=1 in intravenous nivolumab arm and n=3 in placebo arm.

[b] Based on Kaplan-Meier estimates.

[c] Stratified Cox proportional hazard model. Hazard ratio is intravenous nivolumab over placebo.

[d] Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status, PD-L1 status (≥1% vs <1%/indeterminate). Boundary for statistical significance in all randomized patients: p-value <0.01784.

[e] Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status. Boundary for statistical significance in all randomized patients with PD-L1 ≥1%: p-value <0.01282.

Figure 17: Disease-free Survival in All Randomized Patients - CHECKMATE-274

First-line Treatment of Unresectable or Metastatic UC

The effectiveness of OPDIVO QVANTIG has been established for the first-line treatment of unresectable or metastatic UC in combination with cisplatin and gemcitabine. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this UC population.

CHECKMATE-901

CHECKMATE-901 (NCT 03036098) was a randomized, open-label study in patients with previously untreated unresectable or metastatic UC. Prior neoadjuvant or adjuvant chemotherapy were permitted as long as the disease recurrence took place ≥12 months from completion of therapy. Patients who were ineligible for cisplatin and those with active CNS metastases were excluded. Stratification factors for randomization were PD-L1 status (≥1% vs. <1% or indeterminate) and liver metastasis. Patients were randomized 1:1 to receive either:

- Intravenous nivolumab 360 mg and cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle for up to 6 cycles followed by

single-agent intravenous nivolumab 480 mg every 4 weeks until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, intravenous nivolumab was continued for up to 2 years from first dose.
- Cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle for up to 6 cycles, until disease progression or unacceptable toxicity.

The major efficacy outcome measures were OS and PFS as assessed by BICR using RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.

The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥65 years of age and 12% of patients ≥75 years of age, 23% were Asian, 72% were White, 0.3% were Black, 0.3% were American Indian or Alaska Native, 4.9% were Other, 12% were Hispanic or Latino, and 77% were male. Baseline ECOG performance status was 0 (53%) or 1 (46%). At baseline, 87% of patients had metastatic UC, including 20% with liver metastases, 11% had locally advanced UC, and 51% had UC histologic variants. Forty-nine (16%) in the intravenous nivolumab in combination with cisplatin-based chemotherapy arm and 43 (14%) in the cisplatin-based chemotherapy arm switched from cisplatin to carboplatin after at least one cycle of cisplatin.

Efficacy results are presented in Table 63 and Figures 18 and 19.

Table 63: Efficacy Results – CHECKMATE-901

	Intravenous Nivolumab and Cisplatin and Gemcitabine (n=304)	**Cisplatin and Gemcitabine (n=304)**
Overall Survival (OS)		
Events, n (%)	172 (56.6)	193 (63.5)
Median (months) (95% CI)[a]	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival (PFS)[d]		
Events, n (%)	211 (69.4)	191 (62.8)
Median (months) (95% CI)[a]	7.9 (7.6, 9.5)	7.6 (6.0, 7.8)
Hazard ratio (95% CI)[b]	0.72 (0.59, 0.88)	
p-value[c]	0.0012	
Objective Response Rate (ORR)[d]		
Response rate, n (%) (95% CI)	175 (57.6%) (51.8, 63.2)	131 (43.1%) (37.5, 48.9)
Complete response rate, n (%)	66 (22%)	36 (12%)
Partial response rate, n (%)	109 (36%)	95 (31%)
Duration of Response (DoR)		
Median (months) (95% CI)[a]	9.5 (7.6, 15.1)	7.3 (5.7, 8.9)

[a] Based on Kaplan-Meier Estimates.

[b] Stratified Cox proportional hazard model.
[c] 2 sided p values from stratified log-rank test.
[d] Assessed by BICR.

Figure 18: Overall Survival - CHECKMATE-901

Figure 19: Progression-free Survival - CHECKMATE-901

Previously Treated Advanced or Metastatic Urothelial Carcinoma

The effectiveness of OPDIVO QVANTIG has been established for the treatment of patients with locally advanced or metastatic UC and disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this UC population.

CHECKMATE-275

CHECKMATE-275 (NCT02387996) was a single-arm trial in 270 patients with locally advanced or metastatic UC who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first

48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRRC using RECIST v1.1 and DOR.

The median age was 66 years (range: 38 to 90), 78% were male, 86% were White. Twenty-seven percent had non-bladder urothelial carcinoma and 84% had visceral metastases. Thirty-four percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy. Twenty-nine percent of patients had received ≥2 prior systemic regimens in the metastatic setting. Thirty-six percent of patients received prior cisplatin only, 23% received prior carboplatin only, and 7% were treated with both cisplatin and carboplatin in the metastatic setting. Forty-six percent of patients had an ECOG performance status of 1. Eighteen percent of patients had a hemoglobin <10 g/dL, and twenty-eight percent of patients had liver metastases at baseline. Patients were included regardless of their PD-L1 status.

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are shown in Table 64. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 64: Efficacy Results - CHECKMATE-275

	All Patients N=270	**PD-L1 <1% N=146**	**PD-L1 ≥1% N=124**
Confirmed Overall Response Rate, n (%) (95% CI)	53 (19.6%) (15.1, 24.9)	22 (15.1%) (9.7, 21.9)	31 (25.0%) (17.7, 33.6)
Complete response rate	7 (2.6%)	1 (0.7%)	6 (4.8%)
Partial response rate	46 (17.0%)	21 (14.4%)	25 (20.2%)
Median Duration of Response[a] (months) (range)	10.3 (1.9+, 12.0+)	7.6 (3.7, 12.0+)	NR[b] (1.9+, 12.0+)

[a] Estimated from the Kaplan-Meier Curve.

[b] Not Reached.

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

Treatment of MSI-H or dMMR mCRC

The effectiveness of OPDIVO QVANTIG has been established for the treatment of unresectable or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC) in adult and pediatric patients 12 years and older who weigh 30 kg or greater following treatment with intravenous nivolumab and ipilimumab combination therapy.

Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab (CHECKMATE-8HW, NCT03143153), and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and

intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this CRC population.

CHECKMATE-8HW

CHECKMATE-8HW (NCT03143153) was a randomized, 3-arm, open-label trial in immunotherapy-naive patients across all lines of therapy with unresectable or metastatic CRC with known tumor MSI-H or dMMR (MSI-H/dMMR) status as determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumor specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary study population.

The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors.

Patients were randomized to receive one of the following treatments:

- Intravenous nivolumab 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then intravenous nivolumab 480 mg every 4 weeks.
- Intravenous nivolumab 240 mg every 2 weeks for 6 doses, then intravenous nivolumab 480 mg every 4 weeks.
- Investigator’s choice chemotherapy
    - mFOLFOX6 (oxaliplatin, leucovorin, and FU) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus followed by FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks.
    - FOLFIRI (irinotecan, leucovorin, and FU) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus and FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks.

Randomization was stratified by tumor location (right vs left) and by prior lines of therapy (0, 1, 2L+). Patients randomized to the chemotherapy arm could receive intravenous nivolumab in combination with ipilimumab upon progression assessed by BICR.

Study treatment was administered until disease progression, unacceptable toxicity, or for up to 2 years for patients who received intravenous nivolumab plus ipilimumab or intravenous nivolumab monotherapy. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue intravenous nivolumab as a single agent. Intravenous nivolumab with or without ipilimumab could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumor assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter up until week 96, then every 16 weeks thereafter up until week 144, and then every 24 weeks.

The evaluation of efficacy relied on the comparison of patients with centrally confirmed

MSI-H/dMMR mCRC randomized to intravenous nivolumab in combination with ipilimumab versus chemotherapy in the first line (1L) setting and the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to intravenous nivolumab plus ipilimumab vs intravenous nivolumab in all lines setting.

The major efficacy outcome measure was BICR-assessed PFS per RECIST 1.1. Additional efficacy outcome measures included ORR and duration of response assessed by BICR and OS.

The baseline characteristics of the total of 839 patients randomized were: the median age was 63 years (range: 20 to 87), with 46% ≥65 years of age and 14% ≥75 years of age; 50% were male and 87% were White, 9.3% were Asian, 1.5% Black or African American, and 2.3% other race; 9.2% were Hispanic or Latino, 50% Not Hispanic or Latino, 41% ethnicity unknown. Baseline ECOG performance status was 0 (52%) and 1 (48%); number of prior lines of therapy was 0 (56%), 1 (24%), and ≥2 (19%); and tumor location was right-sided or left-sided for 69% and 31% of patients, respectively. The baseline characteristics in patients with centrally confirmed MSI-H/dMMR is consistent with that of all randomized patients.

First-Line intravenous nivolumab in combination with ipilimumab

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

In the 1L setting 200 of 202 patients assigned to receive intravenous nivolumab combined with ipilimumab and 88 of 101 patients assigned to receive chemotherapy received at least 1 dose of study treatment. Among the 88 patients who received chemotherapy, 58% and 42% of patients received oxaliplatin-containing regimens and irinotecan-containing regimens, respectively, and 66 (75%) patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

The BICR-assessed PFS efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the intravenous nivolumab and ipilimumab arm compared with chemotherapy in the 1L setting are presented in Table 65 and Figure 20. The comparative results of ORR and OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 65: Efficacy Results, First-Line - CHECKMATE-8HW

	Intravenous Nivolumab and Ipilimumab (n=171)	**Chemotherapy (n=84)**
Progression-free Survival		
Disease progression or death (%)	48 (28)	52 (62)
Median in months[b] (95% CI)	NR (38.4, NE)	5.8 (4.4, 7.8)
Hazard ratio[c] (95% CI)	0.21 (0.14, 0.32)	
p-value[a]	<0.0001	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 6.1 months at data cutoff date 12Oct2023.
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional

hazards model. The p-value threshold for statistical significance was 0.0209.
[b] Based on Kaplan-Meier estimates.
[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) per IRT.

Figure 20: Progression-free Survival (First-Line Intravenous Nivolumab + Ipilimumab vs Chemotherapy) - CHECKMATE-8HW

All lines intravenous nivolumab in combination with ipilimumab

Among 707 patients across all treatment lines who were randomly assigned to intravenous nivolumab in combination with ipilimumab (354) and to intravenous nivolumab (353) single agent, 296 and 286 patients had centrally confirmed MSI-H/dMMR status in the intravenous nivolumab in combination with ipilimumab arm and in the intravenous nivolumab arm, respectively. Patients receiving at least 1 dose of study treatment included 352 of 354 patients randomized to intravenous nivolumab in combination with ipilimumab, and 351 of 353 patients randomized to single agent intravenous nivolumab.

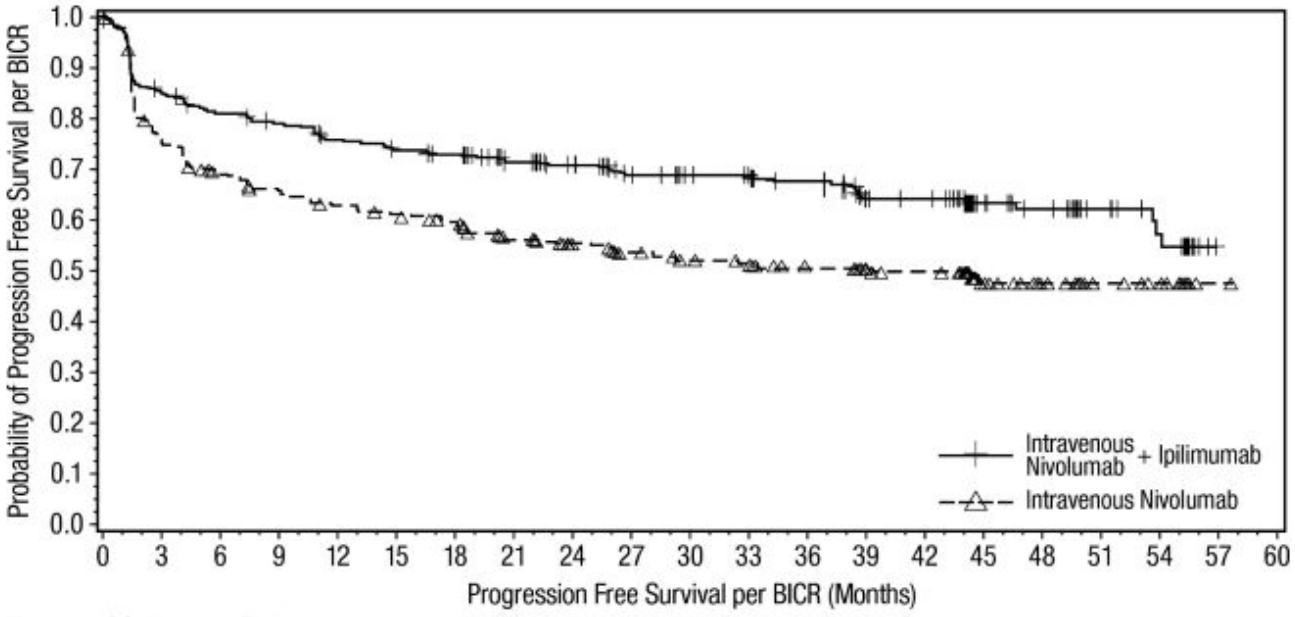
The BICR-assessed PFS and ORR efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the intravenous nivolumab in combination with ipilimumab compared with intravenous nivolumab single agent across all treatment lines setting are presented in Table 66 and Figure 21. The comparative results of OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 66: Efficacy Results, All Lines - CHECKMATE-8HW

	Intravenous Nivolumab and Ipilimumab (n=296)	Intravenous Nivolumab (n=286)
Progression-free Survival		
Disease progression or death n (%)	101 (34)	136 (48)
Median (months)[b] (95% CI)	NR (53.8, NE)	39.3 (22.1, NE)
Hazard ratio[c] (95% CI)	0.62 (0.48, 0.81)	
p-value[a]	0.0003	
Objective Response Rate (ORR)		
Response Rate, n (%) (95% CI)	209 (71%) (65, 76)	165 (58%) (52, 63)
Complete Response Rate, n (%)	90 (30%)	80 (28%)
Partial Response Rate, n (%)	119 (40%)	85 (30%)
p-value[d]	0.0011	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 16.7 months at data cutoff date 28Aug2024.
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0095.
[b] Based on Kaplan-Meier estimates.
[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥2) per IRT.
[d] Based on Cochran-Mantel-Haenszel test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.006.

Figure 21: Progression-free Survival (All lines Intravenous Nivolumab + Ipilimumab vs Intravenous Nivolumab) - CHECKMATE-8HW



Number of Subjects at Risk

Arm A: Intravenous Nivolumab

286	210	191	179	169	164	158	141	124	109	98	95	81	72	69	39	31	15	12	1	0

Arm B: Intravenous Nivolumab + Ipilimumab

296	248	234	225	214	207	200	180	164	146	136	134	121	102	100	61	54	29	23	0	0

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

The effectiveness of OPDIVO QVANTIG has been established for the treatment of microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan in adult and pediatric patients 12 years and older who weigh 30 kg or greater. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab (CHECKMATE-142, NCT02060188), and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this CRC population.

CHECKMATE-142

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine- , oxaliplatin- , or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG performance status 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients enrolled in the single agent intravenous nivolumab MSI-H mCRC cohort received nivolumab 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the intravenous nivolumab and ipilimumab MSI-H mCRC cohort received nivolumab 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by nivolumab as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment

in both cohorts continued until unacceptable toxicity or radiographic progression.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included ORR and DOR as assessed by BICR using RECIST v1.1.

A total of 74 patients were enrolled in the single-agent MSI-H mCRC intravenous nivolumab cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were White. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 7%, 30%, 28%, 19%, and 16% received 0, 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

A total of 119 patients were enrolled in the intravenous nivolumab and ipilimumab MSI-H mCRC cohort. The median age was 58 years (range: 21 to 88), with 32% ≥65 years of age and 9% ≥75 years of age; 59% were male and 92% were White. Baseline ECOG performance status was 0 (45%) and 1 (55%), and 29% were reported to have Lynch Syndrome. Across the 119 patients, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 10%, 40%, 24%, and 15% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results for each of these single-arm cohorts are shown in Table 67.

Table 67: Efficacy Results - CHECKMATE-142

	Intravenous Nivolumab[a] MSI-H/dMMR Cohort		**Intravenous Nivolumab and Ipilimumab[b] MSI-H/dMMR Cohort**	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
Overall Response Rate per BICR; n (%)	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI)[c]	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
Duration of Response				
Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

[a] Minimum follow-up 33.7 months for all patients treated with intravenous nivolumab (n=74).
[b] Minimum follow-up 27.5 months for all patients treated with intravenous nivolumab and ipilimumab (n=119).
[c] Estimated using the Clopper-Pearson method.

14.10 Hepatocellular Carcinoma

First-Line Treatment of Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

The effectiveness of OPDIVO QVANTIG has been established for the treatment of hepatocellular carcinoma following treatment with intravenous nivolumab and ipilimumab combination therapy. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this hepatocellular carcinoma population.

CHECKMATE-9DW (NCT04039607) was a randomized (1:1), open-label trial in adults (18 years of age or older) with unresectable or metastatic HCC. Patients had histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrollment. The trial excluded patients with active autoimmune disease, brain or leptomeningeal metastases, a history of hepatic encephalopathy (within 12 months of randomization), a platelet count <60,000, clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV).

Patients were randomized to receive either:

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

Randomization was stratified by etiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥400 or <400 ng/mL). Study treatment for intravenous nivolumab in combination with ipilimumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue intravenous nivolumab as a single agent. Treatment beyond RECIST 1.1 defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of

subsequent therapy. The primary efficacy outcome measure was OS in all randomized patients. Additional efficacy measures included BICR-assessed ORR and DOR based on RECIST 1.1 criteria.

A total of 668 patients were randomized to receive intravenous nivolumab in combination with ipilimumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. The trial population characteristics were median age 66 years (range: 20 to 89), with 53% ≥65 years old; 82% male; 53% White, 44% Asian, 2.2% Black; 12% Hispanic or Latino, 48% Not Hispanic or Latino, 40% not reported. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection.

Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and 7 were 77%, 20%, and 3%, respectively; 1 patient with Child Pugh 8 was enrolled. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥400 µg/L.

CHECKMATE-9DW demonstrated a statistically significant improvement in OS and ORR. The minimum follow-up was 26.8 months. Efficacy results are shown in Table 68 and Figure 22.

Table 68: Efficacy Results - CHECKMATE-9DW

	Intravenous Nivolumab 1 mg/kg and Ipilimumab (n=335)	**Lenvatinib or Sorafenib (n=333)**
Overall Survival		
Deaths (%)	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI)[a]	0.79 (0.65, 0.96)	
p-value[b]	0.0180	
Overall Response Rate, n (%)[c]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[d]	<0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[c]		
Median (95% CI)	30.4 (21.2, NR[e])	12.9 (10.2, 31.2)
Range	1.5+, 36.9+	2.1+, 32.5+

[a] Based on stratified Cox proportional hazard model.

[b] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257.

[c] Assessed by BICR using RECIST 1.1.

[d] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical

significance: p-value ≤0.025.
[e] NR: Not Reached
+ Censored observation.

Figure 22: Overall Survival - CHECKMATE-9DW

Previously Treated Hepatocellular Carcinoma

The effectiveness of OPDIVO QVANTIG has been established for the treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have been previously treated with sorafenib following treatment with intravenous nivolumab and ipilimumab. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of this adequate and well-controlled study of intravenous nivolumab in this hepatocellular carcinoma population.

CHECKMATE-040

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of intravenous nivolumab as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV)

and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and then every 12 weeks thereafter. The major efficacy outcome measure was confirmed overall response rate as assessed by BICR using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

The efficacy of intravenous nivolumab in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received intravenous nivolumab 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent intravenous nivolumab at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 69. The results for intravenous nivolumab in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table 69: Efficacy Results - Cohort 4 of CHECKMATE-040

	Intravenous Nivolumab and Ipilimumab (Cohort 4) (n=49)
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)
(95% CI)[b]	(20, 48)
Complete response	4 (8%)
Partial response	12 (24%)
Duration of Response per BICR,[a] RECIST v1.1	n=16
Range (months)	4.6, 30.5+
Percent with duration ≥6 months	88%
Percent with duration ≥12 months	56%
Percent with duration ≥24 months	31%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)
(95% CI)[b]	(22, 50)
Complete response	6 (12%)
Partial response	11 (22%)

[a] Confirmed by BICR.
[b] Confidence interval is based on the Clopper and Pearson method.

14.11 Esophageal Cancer

Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

The effectiveness of OPDIVO QVANTIG has been established for the adjuvant treatment of resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy (CRT). Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this esophageal or gastroesophageal junction cancer population.

CHECKMATE-577

CHECKMATE-577 (NCT02743494) was a randomized, multicenter, double-blind trial in 794 patients with completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following concurrent chemoradiotherapy (CRT). Patients were randomized (2:1) to receive either nivolumab 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Treatment was until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. Enrollment required complete resection within 4 to 16 weeks prior to randomization. The trial excluded patients who did not receive CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Randomization was stratified by tumor PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). The major efficacy outcome measure was disease-free survival (DFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant from the primary resected site) or death, from any cause, whichever occurred first as assessed by the investigator prior to subsequent anti-cancer therapy. Patients on treatment underwent imaging for tumor recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

The trial population characteristics were: median age 62 years (range: 26 to 86), 36% were ≥65 years of age, 85% were male, 15% were Asian, 82% were White, and 1.1% were Black. Disease characteristics were AJCC Stage II (35%) or Stage III (65%) at initial diagnosis carcinoma, EC (60%) or GEJC (40%) at initial diagnosis, with pathologic positive lymph node status (58%) at study entry and histological confirmation of predominant adenocarcinoma (71%) or squamous cell carcinoma (29%). The baseline Tumor PD-L1 status ≥1% was positive for 16% of patients and negative for 72% of patients. Baseline ECOG performance status was 0 (58%) or 1 (42%).

CHECKMATE-577 demonstrated a statistically significant improvement in DFS for patients randomized to the intravenous nivolumab arm as compared with the placebo arm. DFS benefit was observed regardless of tumor PD-L1 expression and histology.

Efficacy results are shown in Table 70 and Figure 23.

Table 70: Efficacy Results - CHECKMATE-577

	Intravenous Nivolumab (n=532)	Placebo (n=262)
Disease-free Survival		
Number of events, n (%)	241 (45%)	155 (59%)
Median (months) (95% CI)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)
Hazard ratio[a] (95% CI)	0.69 (0.56, 0.85)	
p-value[b]	0.0003	

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

Figure 23: Disease-free Survival - CHECKMATE-577

First-line Treatment of Unresectable Advanced or Metastatic Esophageal Squamous Cell Carcinoma (ESCC) Whose Tumors Express PD-L1 (≥1)

The effectiveness of OPDIVO QVANTIG in combination with fluoropyrimidine- and

platinum-containing chemotherapy has been established for the first-line treatment of unresectable advanced or metastatic ESCC. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this esophageal squamous cell carcinoma population.

CHECKMATE-648

CHECKMATE-648 (NCT03143153) was a randomized, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC (squamous or adenosquamous histology). The trial enrolled patients whose tumor was evaluable for tumor cell (TC) PD-L1 expression [also called PD-L1 tumor proportion score (TPS)], which was evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. A retrospective scoring of a patient's tumor PD-L1 status using Combined Positive Score (CPS), was also conducted using the PD-L1-stained tumor specimens used for randomization. Patients were not amenable to chemoradiation or surgery with curative intent. Prior treatment with curative intent was allowed if completed more than six months prior to trial enrollment. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. Patients were randomized to receive one of the following treatments:

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

Patients received intravenous nivolumab until disease progression, unacceptable toxicity, or up to 2 years. In patients who received intravenous nivolumab in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue intravenous nivolumab as a single agent.

Randomization was stratified by TC PD-L1 expression (≥1% vs. <1% or indeterminate), region (East Asia vs. Rest of Asia vs. Rest of World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2). The major efficacy outcome measures were OS and BICR-assessed PFS in patients with TC PD-L1 expression ≥1%. Additional efficacy measures included OS in all randomized patients, BICR-assessed PFS in all randomized patients, and ORR assessed by BICR in TC PD-L1 expression ≥1% and in all randomized patients. The tumor assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 970 patients were randomized in CHECKMATE-648 study among whom 965 and 906 patients had quantifiable TC PD-L1 expression and CPS at baseline, respectively; 85% (824/970) had tumors with PD-L1 CPS ≥1. The trial population characteristics in patients with PD-L1 CPS ≥1 were median age 63 years (range: 26 to 90), 46% were ≥65

years of age, 82% were male, 71% were Asian, 25% were White, and 1.2% were Black or African American. Patients had histological confirmation of squamous cell carcinoma (99%) or adenosquamous cell carcinoma (1.7%) in the esophagus. Baseline ECOG performance status was 0 (44.0%) or 1 (54%).

A statistically significant improvement in OS was demonstrated in patients randomized to intravenous nivolumab in combination with chemotherapy and patients randomized to intravenous nivolumab in combination with ipilimumab compared with chemotherapy. An exploratory analysis of OS in patients with PD-L1 CPS <1 showed a HR of 0.98 (95% CI 0.50, 1.95) for the comparison of intravenous nivolumab in combination with chemotherapy, and the exploratory analysis OS in patients with PD-L1 CPS <1 showed a HR of 1.0 (95% CI 0.52, 1.94) for the comparison of intravenous nivolumab in combination with ipilimumab; these results indicate that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1. Efficacy results are shown in Table 71 and Figures 24 and 25.

Table 71: Efficacy Results - CHECKMATE-648

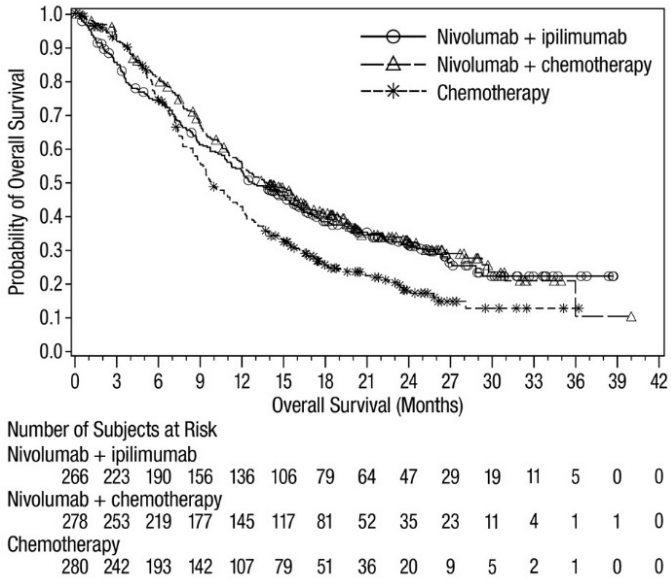
	Intravenous Nivolumab with Cisplatin and Fluorouracil (n=158)	**Intravenous Nivolumab and Ipilimumab (n=158)**	**Cisplatin and Fluorouracil (n=157)**	**Intravenous Nivolumab with Cisplatin and Fluorouracil (n=278)**	**Intravenous Nivolumab and Ipilimumab (n=266)**	**Cisplatin and Fluorouracil (n=280)**
	TC PD-L1 expression ≥1%			**PD-L1 CPS ≥1**		
Overall Survival						
Deaths (%)	98 (62)	106 (67)	121 (77)	177 (64)	179 (67)	205 (73)
Median (months) (95% CI)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)	13.8 (12.0, 16.1)	12.7 (10.9, 15.5)	9.8 (8.8, 11.6)
Hazard ratio (95% CI)[b]	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-	0.69 (0.57, 0.85)	0.76 (0.62, 0.93)	-
p-value[c]	<0.0001[S1]	0.0010[S2]	-	-	-	-
Progression-free Survival[a]						
Disease progression or death (%)	117 (74)	123 (78)	100 (64)	201 (72)	206 (77)	184 (66)
Median (months) (95% CI)	6.9 (5.7, 8.3)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)	5.8 (5.5, 7.0)	2.8 (2.6, 4.2)	5.6 (4.2, 5.9)
Hazard ratio (95% CI)[b]	0.65 (0.49, 0.86)	1.02 (0.78, 1.34)	-	0.8 (0.7, 1.0)	1.2 (1.0, 1.5)	-
p-value[c]	0.0023[S3]	NS	-	-	-	-
Overall Response	84 (53.2)	56 (35.4)	31 (19.7)	135 (49)	74 (28)	76 (27)

Rate, n (%)[a, NT]						
(95% CI)	(45.1, 61.1)	(28.0, 43.4)	(13.8, 26.8)	(42.5, 54.6)	(22.5, 33.6)	(22.0, 32.8)
Complete response (%)	26 (16.5)	28 (17.7)	8 (5.1)	39 (14)	32 (12.0)	18 (6.4)
Partial response (%)	58 (36.7)	28 (17.7)	23 (14.6)	96 (35)	42 (15.8)	58 (20.7)
Duration of Response (months)[a]						
Median (95% CI)	8.4 (6.9, 12.4)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)	8.2 (6.7, 11.1)	11.8 (7.1, 23.6)	6.9 (5.7, 8.2)
Range	1.4+, 34.6	1.4+, 34.5+	1.4+, 31.8+	1.4+, 35.9+	1.4+, 34.5+	1.4+, 31.8+

[a] Assessed by BICR.
[b] Based on stratified Cox proportional hazard model. Hazard ratios are reported for each intravenous nivolumab containing arm compared to chemotherapy within each analysis population.
[c] Based on a stratified 2-sided log-rank test.
[S1, S2, S3] Significant p-value compared to stopping boundary of 0.005, 0.014, and 0.015, respectively.
NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure.

Figure 24: Overall Survival – CHECKMATE-648

(A) OS in CPS ≥1



(B) OS in TC PD-L1 ≥1%

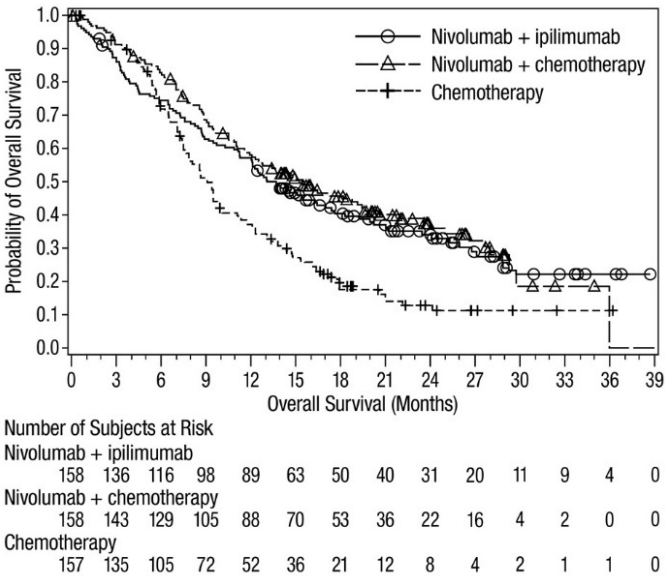
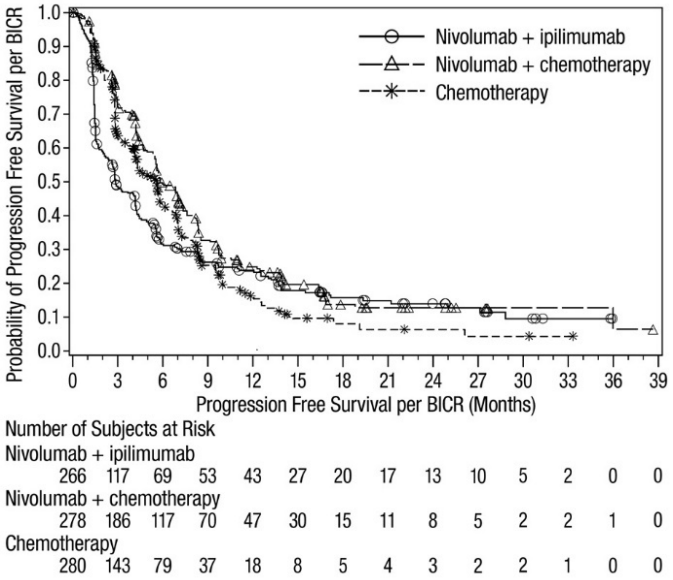
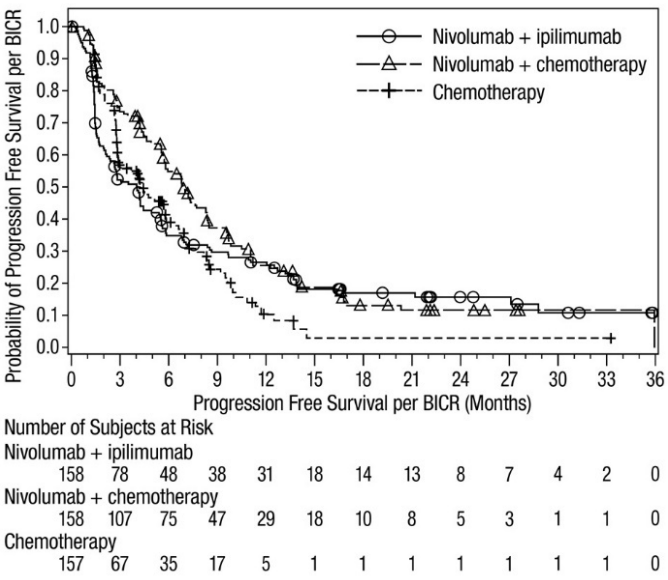


Figure 25: Progression-free Survival – CHECKMATE-648

(A) PFS in CPS ≥1

(B) PFS in TC PD-L1 ≥1%





Previously Treated Unresectable Advanced, Recurrent or Metastatic ESCC

The effectiveness of OPDIVO QVANTIG has been established for the treatment of unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this ESCC population.

ATTRACTION-3

ATTRACTION-3 (NCT02569242) was a multicenter, randomized (1:1), active-controlled, open-label trial in patients with unresectable advanced, recurrent, or metastatic ESCC, who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen. The trial enrolled patients regardless of PD-L1 status, but tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, or had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients were randomized to receive nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m^2 intravenously every 3 weeks) or paclitaxel (100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off).

Randomization was stratified by region (Japan vs. Rest of World), number of organs with metastases (≤1 vs. ≥2), and PD-L1 status (≥1% vs. <1% or indeterminate). Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. The tumor assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were ORR and PFS as assessed by the investigator using RECIST v1.1 and DOR.

A total of 419 patients were randomized; 210 to the intravenous nivolumab arm and 209 to the investigator's choice arm (docetaxel: 31%, paclitaxel: 69%). The trial population characteristics were: median age 65 years (range: 33 to 87), 53% were ≥65 years of age, 87% were male, 96% were Asian and 4% were White. Sixty-seven percent of patients had received one prior systemic therapy regimen and 26% had received two prior systemic therapy regimens prior to enrolling in ATTRACTION-3. Baseline ECOG performance status was 0 (50%) or 1 (50%).

ATTRACTION-3 demonstrated a statistically significant improvement in OS for patients randomized to intravenous nivolumab as compared with investigator's choice of taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. OS results by PD-L1 CPS level (<1 and ≥1) were not studied. The minimum follow-up was 17.6 months. Efficacy results are shown in Table 72 and Figure 26.

Table 72: Efficacy Results - ATTRACTION-3

	Intravenous Nivolumab (n=210)	**Docetaxel or Paclitaxel (n=209)**
Overall Survival[a]		
Deaths (%)	160 (76%)	173 (83%)
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Overall Response Rate[d]	33 (19.3)	34 (21.5)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response (%)	1 (0.6)	2 (1.3)
Partial response (%)	32 (18.7)	32 (20.3)
Median duration of response (months) (95% CI)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
p-value[e]	0.6323	
Progression-free Survival[a, f]		
Disease progression or death (%)	187 (89)	176 (84)
Median (months) (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	

[a] Based on ITT analysis.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] Based on Response Evaluable Set (RES) analysis, n=171 in intravenous nivolumab group and n=158 in investigator's choice group.
[e] Based on stratified Cochran-Mantel-Haenszel test; p-value not significant.
[f] PFS not tested due to pre-specified hierarchical testing strategy.

Figure 26: Overall Survival - ATTRACTION-3

Of the 419 patients, 48% had PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. The remaining 52% had PD-L1 negative ESCC defined as <1% of tumor cells expressing PD-L1.

In a pre-specified exploratory analysis by PD-L1 status, the hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the intravenous nivolumab and investigator's choice arms, respectively, in the PD-L1 positive subgroup. In the PD-L1 negative subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the intravenous nivolumab and investigator's choice arms, respectively.

14.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma Whose Tumors Express PD-L1 (≥1)

The effectiveness of OPDIVO QVANTIG in combination with fluoropyrimidine- and platinum-containing chemotherapy has been established for the treatment of gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. Use of OPDIVO QVANTIG for this indication is supported by evidence from an adequate and well-controlled study conducted with intravenous nivolumab, and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Below is a description of the efficacy results of the adequate and well-controlled study of intravenous nivolumab in this

population.

CHECKMATE-649

CHECKMATE-649 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory (tumor cell [TC] and Combined Positive Score [CPS]). The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive intravenous nivolumab in combination with chemotherapy (n=789) or chemotherapy (n=792). Patients received one of the following treatments:

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

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received intravenous nivolumab in combination with chemotherapy and in whom chemotherapy was discontinued, intravenous nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation.

Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (mFOLFOX6 vs. CapeOX). The major efficacy outcome measures, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Additional efficacy outcome measures included OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and ORR and DOR as assessed by BICR in patients with PD-L1 CPS ≥1 and ≥5, and in all randomized patients. Tumor assessments were conducted per RECIST v1.1 every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 1581 patients were randomized in the CHECKMATE-649 study, among whom 1296 and 955 had baseline PD-L1 CPS ≥1 and CPS ≥5, respectively. The trial population characteristics in patients with PD-L1 CPS ≥1 were: median age 62 years (range: 18 to 90), 40% were ≥65 years of age, 72% were male, 23% were Asian, and 69% were White, and 1% were Black or African American. Baseline ECOG performance status was 0 (42%) or 1 (58%). Seventy percent of patients had adenocarcinoma tumors in the stomach, 17% in the gastroesophageal junction, and 13% in the esophagus.

CHECKMATE-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients and patients with PD-L1 CPS ≥1. Exploratory analysis of OS in the CPS <1 population showed a hazard ratio of 0.85 (95% CI: 0.63, 1.15), indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 73 and Figures 27 and 28.

Table 73: Efficacy Results - CHECKMATE-649

	Intravenous	**mFOLFOX6**	**Intravenous**	**mFOLFOX6**

	Nivolumab and mFOLFOX6 or CapeOX (n=641)	or CapeOX (n=655)	Nivolumab and mFOLFOX6 or CapeOX (n=473)	or CapeOX (n=482)
	PD-L1 CPS ≥1		PD-L1 CPS ≥5	
Overall Survival				
Deaths (%)	434 (68)	492 (75)	309 (65)	362 (75)
Median (months) (95% CI)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (95% CI)[a]	0.77 (0.68, 0.88)		0.71 (0.61, 0.83)	
p-value[b]	<0.0001		<0.0001	
Progression-free Survival[c]				
Disease progression or death (%)	454 (70.8)	472 (72.1)	328 (69.3)	350 (72.6)
Median (months) (95% CI)	7.5 (7.0, 8.4)	6.9 (6.1, 7.0)	7.7 (7.0, 9.2)	6.0 (5.6, 6.9)
Hazard ratio (95% CI)[a]	0.74 (0.65, 0.85)		0.68 (0.58, 0.79)	
p-value[b]	-[e]		<0.0001	
Overall Response Rate, n (%)[c,d]	314 (49)	249 (38)	237 (50)	184 (38)
(95% CI)	(45, 53)	(34, 42)	(46, 55)	(34, 43)
Complete response (%)	65 (10)	42 (6)	55 (12)	34 (7)
Partial response (%)	249 (39)	207 (32)	182 (38)	150 (31)
Duration of Response (months)[c,d]				
Median (95% CI) Range	8.5 (7.7, 10.3) 1.1+, 29.6+	6.9 (5.8, 7.6) 1.2+, 30.8+	9.5 (8.1, 11.9) 1.1+, 29.6+	6.9 (5.6, 7.9) 1.2+, 30.8+

[a] Based on stratified Cox proportional hazard model.
[b] Based on stratified log-rank test.
[c] Assessed by BICR.
[d] Based on confirmed response.
[e] Not evaluated for statistical significance.

Figure 27: Overall Survival (PD-L1 CPS ≥1) - CHECKMATE-649

Figure 28: Overall Survival (PD-L1 CPS ≥5) - CHECKMATE-649

An exploratory analysis of OS in the 44 patients with MSI-H tumors showed a HR of 0.37 (95% CI: 0.16, 0.87).

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy) injection is a sterile, preservative-free, clear to opalescent and colorless to yellow solution for subcutaneous use. It is supplied as an individually packaged single-dose vial as follows:

Carton Contents	NDC
300 mg nivolumab and 5,000 units hyaluronidase per 2.5 mL (120 mg/2,000 units per mL) single-dose vial	0003-3120-01
600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) single-dose vial	0003-6120-01

Store OPDIVO QVANTIG vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO QVANTIG, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.1)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.1)]*.
- 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)]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.2)]*.

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 (5.3) and Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO QVANTIG and for 5 months following the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO QVANTIG and for 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

U.S. License No. 1713

Halozyme Therapeutics, Inc.
12390 El Camino Real
San Diego, CA 92130

U.S. License No. 2187

MEDICATION GUIDE
OPDIVO QVANTIG™ (op-DEE-voh cue-VAN-tig)
(nivolumab and hyaluronidase-nvhy)
injection, for subcutaneous use

Read this Medication Guide before you start receiving OPDIVO QVANTIG and before each injection. There may be new information. If your healthcare provider prescribes OPDIVO QVANTIG in combination with cabozantinib, also read the Patient Information that comes with cabozantinib. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OPDIVO QVANTIG?

OPDIVO QVANTIG is a medicine that may treat certain cancers by working with your immune system. OPDIVO QVANTIG can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. You may have more than one of these problems at the same time. Some of these problems may happen more often when OPDIVO QVANTIG is used in combination with another therapy.

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

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of
- dark urine (tea colored)

your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- bleeding or bruising more easily than normal

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

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

Skin problems.

- rash
- itching
- skin blistering or peeling
- swollen lymph nodes
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with OPDIVO QVANTIG. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Rejection of a transplanted organ or tissue. Your healthcare provider should tell you what signs and symptoms you should report and monitor you depending on the type of organ or tissue transplant that you have had.
Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during treatment with OPDIVO QVANTIG. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO QVANTIG, if you have severe side effects.

What is OPDIVO QVANTIG?
OPDIVO QVANTIG is a prescription medicine used to treat:

- **adults with a type of kidney cancer that has spread called advanced renal cell carcinoma (RCC).**
    - OPDIVO QVANTIG may be used alone as a first treatment in certain people with advanced RCC, after completing combination treatment with nivolumab given into the vein (intravenous nivolumab) and ipilimumab.
    - OPDIVO QVANTIG may be used in combination with cabozantinib as your first treatment when your cancer has spread (advanced RCC).
    - OPDIVO QVANTIG may be used alone when your cancer has spread after treatment with other cancer medicines.
- **adults and children 12 years of age and older who weigh 66 pounds (30 kg) or more with a type of skin cancer called melanoma.**
    - OPDIVO QVANTIG may be used alone to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma).
    - OPDIVO QVANTIG may be used alone to treat melanoma that has spread or cannot be removed by surgery, after completing combination treatment with intravenous nivolumab and ipilimumab.
    - OPDIVO QVANTIG may be used alone to help prevent Stage IIB, Stage IIC, Stage III, or Stage IV melanoma from coming back after it has been completely removed by surgery.
- **adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
    - OPDIVO QVANTIG may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine before you have surgery for early-stage NSCLC.
    - OPDIVO QVANTIG may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine before you have surgery for early-stage NSCLC:
        - that does not have an abnormal EGFR or ALK gene, **and**
        - then OPDIVO QVANTIG may be continued alone after surgery to help prevent your lung cancer from coming back.
    - OPDIVO QVANTIG may be used alone when your lung cancer:
        - has spread, **and**
        - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
        - If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **adults with head and neck cancer (squamous cell carcinoma).**
    - OPDIVO QVANTIG may be used alone when your head and neck cancer:
        - has come back or spread, **and**
        - you have tried chemotherapy that contains platinum and it did not work or is no longer working.

- **adults with cancer of the lining of the urinary tract (urothelial carcinoma).**
    - OPDIVO QVANTIG may be used alone to help prevent cancer of the urinary tract from coming back after it was removed by surgery.
    - OPDIVO QVANTIG may be used in combination with chemotherapy medicines cisplatin and gemcitabine as your first treatment when your urinary tract cancer has spread (metastatic) or cannot be removed by surgery.
    - OPDIVO QVANTIG may be used alone when your urinary tract cancer has spread (locally advanced or metastatic), **and**:
        - you have tried chemotherapy that contains platinum, and it did not work or is no longer working, **or**
        - your cancer worsened within 12 months of treatment with chemotherapy that contains platinum, either before or after surgery to remove your cancer.
- **adults and children 12 years of age and older who weigh 66 pounds (30 kg) or more with a type of colon or rectal cancer (colorectal cancer or CRC).**
    - OPDIVO QVANTIG may be used alone, after completing combination treatment with intravenous nivolumab and ipilimumab, when your colon or rectal cancer:
        - cannot be removed with surgery or has spread, **and**
        - is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
    - OPDIVO QVANTIG may be used alone when your colon or rectal cancer:
        - has spread, **and**
        - is MSI-H or dMMR, **and**
        - you have received treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.
- **adults with a type of liver cancer called hepatocellular carcinoma (HCC).**
    - OPDIVO QVANTIG may be used alone as your first treatment, after completing combination treatment with intravenous nivolumab and intravenous ipilimumab, when your liver cancer:
        - cannot be removed with surgery or has spread.
    - OPDIVO QVANTIG may be used alone, after completing combination treatment with intravenous nivolumab and ipilimumab, when your liver cancer:
        - cannot be removed with surgery or has spread, **and**
        - you have received prior treatment with sorafenib.
- **adults with cancer of the tube that connects your throat to your stomach (esophageal cancer).**
    - OPDIVO QVANTIG may be used alone to help prevent your esophageal or gastroesophageal junction cancer from coming back when:

        - your esophageal or gastroesophageal junction cancer has been treated with chemoradiation followed by surgery to completely remove the cancer, **but**
        - some cancer cells were still present in the removed tumor or lymph nodes.

    - OPDIVO QVANTIG may be used in combination with chemotherapy that contains fluoropyrimidine and platinum as your first treatment when your esophageal cancer:

        - is a type called squamous cell carcinoma, **and**
        - cannot be removed with surgery, or has spread, **and**
        - your tumors are positive for PD-L1.

    - OPDIVO QVANTIG may be used alone when your esophageal cancer:

        - is a type called squamous cell carcinoma, **and**
        - cannot be removed with surgery and has come back or spread, **and**
        - you have received chemotherapy that contains fluoropyrimidine and platinum.

- **adults with cancer of the stomach (gastric cancer), cancer where the esophagus joins the stomach (gastroesophageal junction cancer), and a type of cancer in the esophagus called esophageal adenocarcinoma.**

    - OPDIVO QVANTIG may be used in combination with chemotherapy that contains fluoropyrimidine and platinum when your gastric, gastroesophageal junction, or esophageal cancer:

        - cannot be removed with surgery or has spread, **and**
        - your tumors are positive for PD-L1.

It is not known if OPDIVO QVANTIG is safe and effective in children younger than 12 years of age with melanoma or MSI-H or dMMR metastatic colorectal cancer.
It is not known if OPDIVO QVANTIG is safe and effective in children for the treatment of any other cancers that it is used to treat in adults.

Before receiving OPDIVO QVANTIG, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ or tissue transplant, including corneal transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area in the past and have received other medicines that are like OPDIVO QVANTIG
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. OPDIVO QVANTIG can harm your unborn baby.
  Females who are able to become pregnant:

    - Your healthcare provider should do a pregnancy test before you start receiving OPDIVO QVANTIG.
    - You should use an effective method of birth control during treatment and for

5 months after your last dose of OPDIVO QVANTIG. Talk to your healthcare provider about birth control methods that you can use during this time.
    - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with OPDIVO QVANTIG.

- are breastfeeding or plan to breastfeed. It is not known if OPDIVO QVANTIG passes into your breast milk. Do not breastfeed during treatment and for 5 months after your last dose of OPDIVO QVANTIG.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive OPDIVO QVANTIG?

- Your healthcare provider will give you OPDIVO QVANTIG as an injection under the skin, in the stomach area (abdomen) or thigh, over about 3 to 5 minutes.
- OPDIVO QVANTIG is usually given every 2, 3, or 4 weeks, depending on the dose you are receiving.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- For a type of kidney cancer called advanced renal cell carcinoma, your healthcare provider may also prescribe you cabozantinib. Take cabozantinib exactly as your healthcare provider tells you.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO QVANTIG?
OPDIVO QVANTIG can cause serious side effects, including:

- **See "What is the most important information I should know about OPDIVO QVANTIG?"**
- **Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with OPDIVO QVANTIG. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

The most common side effects of OPDIVO QVANTIG when used alone in people with renal cell carcinoma include:

- pain in muscles, bones, and joints
- feeling tired
- itchy skin
- rash
- low thyroid hormone levels
- diarrhea
- cough
- stomach-area (abdominal) pain

The most common side effects observed with nivolumab given into the vein (intravenous nivolumab), which may be experienced with OPDIVO QVANTIG, are shown below.
The most common side effects of intravenous nivolumab when used alone include:

- feeling tired
- weakness
- upper respiratory tract

- rash
- pain in muscles, bones, and joints
- itching
- diarrhea
- nausea
- cough
- shortness of breath
- constipation
- decreased appetite
- back pain
- infection
- fever
- headache
- stomach-area (abdominal) pain
- vomiting
- urinary tract infection

The most common side effects of intravenous nivolumab when used in combination with cabozantinib as the first treatment for advanced RCC include:

- diarrhea
- feeling tired
- liver problems. See "What is the most important information I should know about OPDIVO QVANTIG?"
- rash, redness, pain, swelling or blisters on the palms of your hands or soles of your feet
- mouth sores
- rash
- high blood pressure
- low thyroid hormone levels
- pain in muscles, bones, and joints
- decreased appetite
- nausea
- change in the sense of taste
- stomach-area (abdominal) pain
- cough
- upper respiratory tract infection

The most common side effects of intravenous nivolumab when used in combination with platinum-containing chemotherapy and another chemotherapy medicine before having surgery for NSCLC include:

- nausea
- constipation
- feeling tired
- decreased appetite
- rash

The most common side effects of intravenous nivolumab when used in combination with cisplatin and gemcitabine to treat urothelial cancer include:

- nausea
- feeling tired
- pain in muscles, bones, and joints
- constipation
- decreased appetite
- rash
- vomiting
- numbness, pain, tingling or burning in your hands and feet

The most common side effects of intravenous nivolumab when used in combination with fluoropyrimidine and platinum-containing chemotherapy to treat esophageal cancer and gastric cancer include:

- nausea
- numbness, pain, tingling, or burning in your hands or feet
- decreased appetite
- feeling tired
- constipation
- mouth sores
- diarrhea
- vomiting
- stomach-area (abdominal) pain
- pain in muscles, bones, and joints

These are not all the possible side effects of OPDIVO QVANTIG.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OPDIVO QVANTIG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about OPDIVO QVANTIG that is written for health professionals.

What are the ingredients in OPDIVO QVANTIG?
Active ingredients: nivolumab and hyaluronidase-nvhy
Inactive ingredients: histidine, histidine hydrochloride monohydrate, methionine, pentetic acid, polysorbate 80, sucrose, and Water for Injection.
Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA U.S. License No. 1713
Halozyme Therapeutics, Inc., 12390 El Camino Real, San Diego, CA 92130, U.S. License No. 2187
OPDIVO QVANTIG™ is a trademark of Bristol-Myers Squibb Company. Other brands listed are the trademarks of their respective owners.
For more information, call 1-855-673-4861 or go to www.Qvantig.com.

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

OPDIVO QVANTIG™ 300 mg and 5,000 units/2.5 mL Representative Packaging

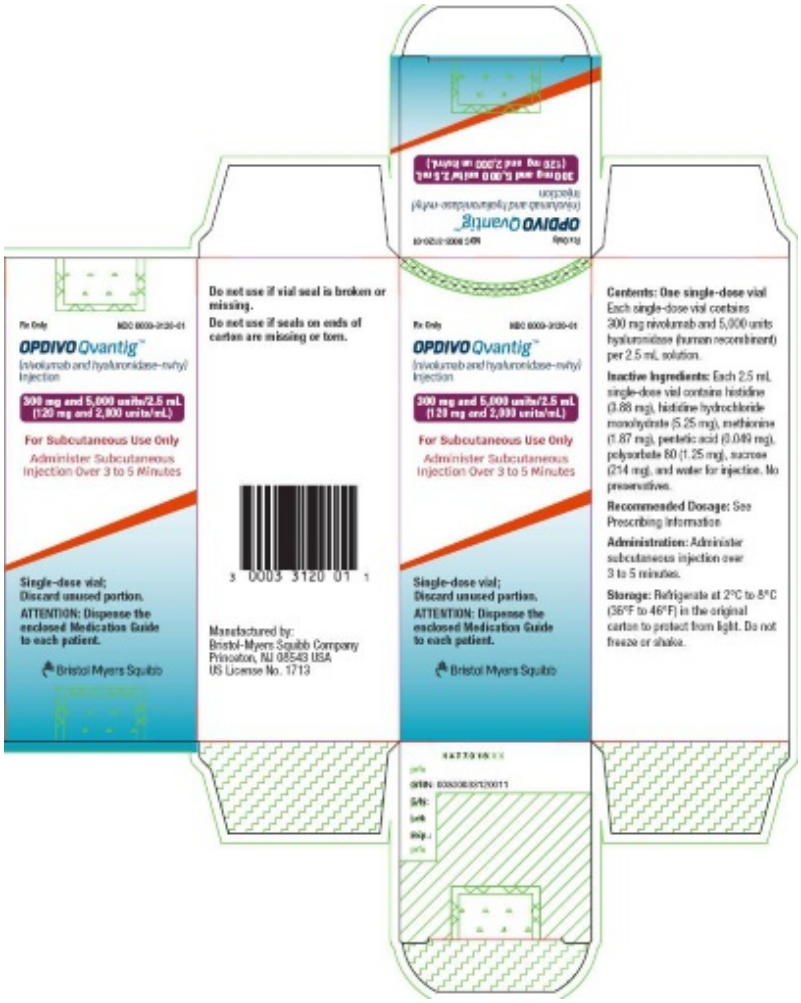
Rx Only
NDC 0003-3120-01

OPDIVO QVANTIG™
(nivolumab and hyaluronidase-nvhy)
injection

300 mg and 5,000 units/2.5 mL
(120 mg and 2,000 units/mL)
For Subcutaneous Use Only
Administer Subcutaneous
Injection Over 3 to 5 Minutes

Single-dose vial;
Discard unused portion.
ATTENTION: Dispense the
enclosed Medication Guide
to each patient.

Bristol Myers Squibb



OPDIVO QVANTIG™ 600 mg and 10,000 units/5 mL Representative Packaging

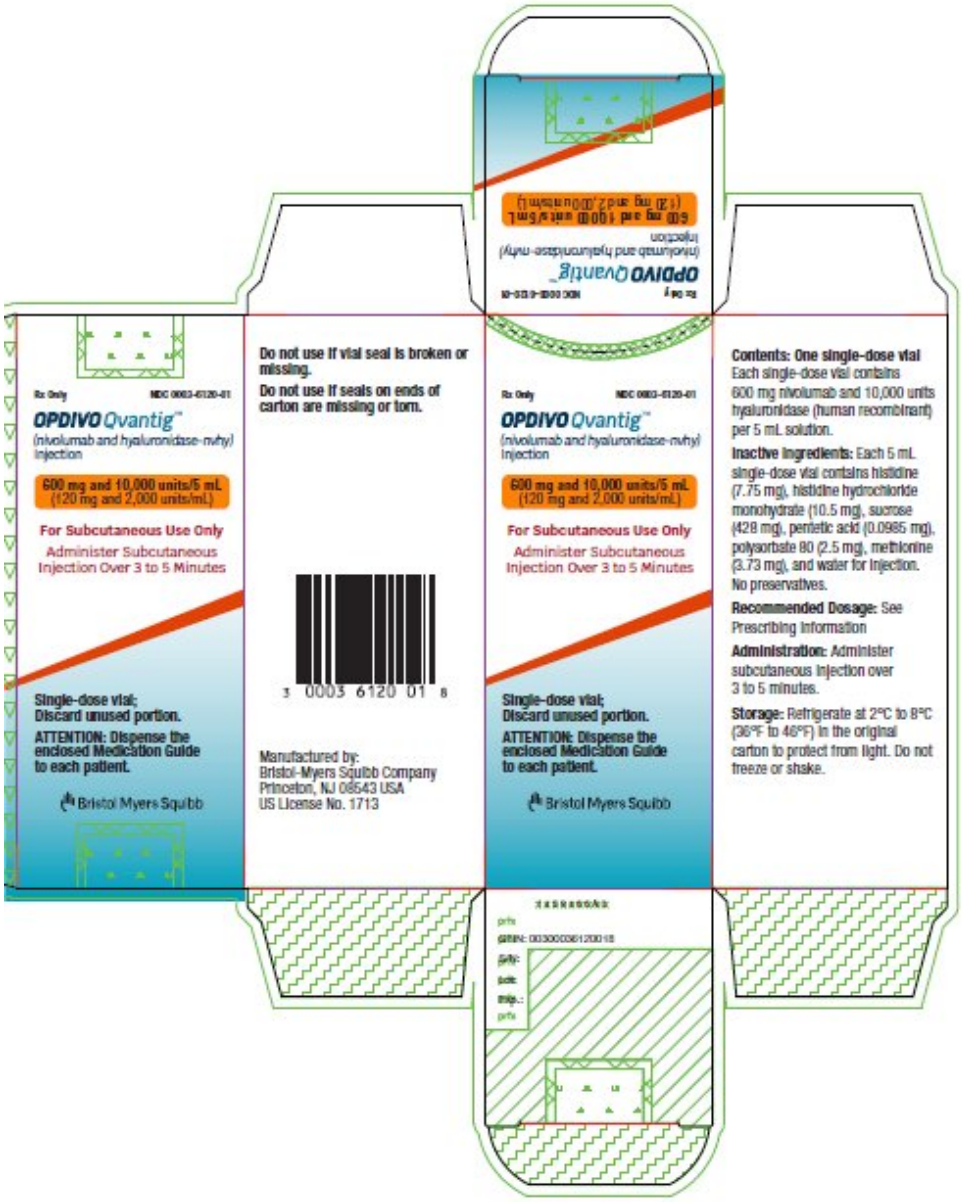
Rx Only
NDC 0003-6120-01

OPDIVO QVANTIG™
(nivolumab and hyaluronidase-nvhy)
injection

600 mg and 10,000 units/5 mL
(120mg and 2,000 units/mL)
For Subcutaneous Use Only
Administer Subcutaneous
Injection Over 3 to 5 Minutes

Single-dose vial;
Discard unused portion.
ATTENTION: Dispense the
enclosed Medication Guide
to each patient.

Bristol Myers Squibb



OPDIVO QVANTIG

nivolumab and hyaluronidase-nvhy injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0003-6120
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NIVOLUMAB (UNII: 31YO63LBSN) (NIVOLUMAB - UNII:31YO63LBSN)	NIVOLUMAB	120 mg in 1 mL
HYALURONIDASE (HUMAN RECOMBINANT) (UNII: 743QUY4VD8) (HYALURONIDASE (HUMAN RECOMBINANT) - UNII:743QUY4VD8)	HYALURONIDASE (HUMAN RECOMBINANT)	2000 U in 1 mL

Inactive Ingredients

Ingredient Name	Strength
HISTIDINE (UNII: 4QD397987E)	1.55 mg in 1 mL
HISTIDINE HYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	2.10 mg in 1 mL
METHIONINE (UNII: AE28F7PNPL)	0.746 mg in 1 mL
PENTETIC ACID (UNII: 7A314HQM0I)	0.0197 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.5 mg in 1 mL
SUCROSE (UNII: C151H8M554)	85.6 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0003-6120-01	1 in 1 CARTON	01/02/2025	
1		5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761381	01/02/2025	

OPDIVO QVANTIG

nivolumab and hyaluronidase-nvhy injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0003-3120
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NIVOLUMAB (UNII: 31YO63LBSN) (NIVOLUMAB - UNII:31YO63LBSN)	NIVOLUMAB	120 mg in 1 mL
HYALURONIDASE (HUMAN RECOMBINANT) (UNII: 743QUY4VD8) (HYALURONIDASE (HUMAN RECOMBINANT) - UNII:743QUY4VD8)	HYALURONIDASE (HUMAN RECOMBINANT)	2000 U in 1 mL

Inactive Ingredients

Ingredient Name	Strength
HISTIDINE (UNII: 4QD397987E)	1.55 mg in 1 mL
HISTIDINE HYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	2.10 mg in 1 mL
METHIONINE (UNII: AE28F7PNPL)	0.746 mg in 1 mL
PENTETIC ACID (UNII: 7A314HQM0I)	0.0197 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.5 mg in 1 mL
SUCROSE (UNII: C151H8M554)	85.6 mg in 1 mL

SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0003-3120-01	1 in 1 CARTON	11/24/2025	
1		2.5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761381	12/27/2024	

Labeler - E.R. Squibb & Sons, L.L.C. (011550092)

Establishment

Name	Address	ID/FEI	Business Operations
BioReliance Ltd.		505004556	ANALYSIS(0003-6120, 0003-3120)

Revised: 11/2025 E.R. Squibb & Sons, L.L.C.