Interactive Dosing Guide

Dosing optimized by indication for your patients

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

OPDIVO® and YERVOY® are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
**OPDIVO® combination indications**

**mMelanoma**
OPDIVO, in combination with YERVOY®, is indicated for the treatment of patients with unresectable or metastatic melanoma.

**HCC**
OPDIVO, in combination with YERVOY, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**MSI-H/dMMR mCRC**
OPDIVO, in combination with YERVOY, is indicated for the treatment of adult and pediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**uMPM**
OPDIVO, in combination with YERVOY®, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM).

**r/m NSCLC**
OPDIVO, in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

**PD-L1 ≥1% mNSCLC**
OPDIVO, in combination with YERVOY, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

**SELECT IMPORTANT SAFETY INFORMATION**

**Infusion-Related Reactions**
- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (56/2207) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 4.2% (5/119) of patients. In patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.
- In separate Phase 3 trials of YERVOY 3 mg/kg and 10 mg/kg monotherapy, infusion-related reactions occurred in 2.9% (28/982) of patients.

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
OPDIVO® combination indications\(^1\) (cont’d)

**OPDIVO**, in combination with YERVOY, is indicated for the first-line treatment of patients with intermediate or poor risk advanced RCC.

**OPDIVO**, in combination with CABOMETYX®, is indicated for the first-line treatment of patients with advanced RCC.

**Advanced or metastatic GC, GEJC, and EAC**

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic GC, GEJC, and EAC.

### Infusion-Related Reactions

**OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.**

- In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.
- In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (60/2470) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (51/974) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (60/2470) of patients.
- In separate Phase 3 trials of YERVOY 3 mg/kg and 10 mg/kg monotherapy, infusion-related reactions occurred in 2.9% (28/982) of patients.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
OPDIVO® monotherapy indications

**Adj tx of melanoma**
OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

**mMelanoma**
OPDIVO, as a single agent, is indicated for the treatment of patients with unresectable or metastatic melanoma.

**mNSCLC**
OPDIVO, as a single agent, is indicated for the treatment of 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.

**aRCC**
OPDIVO, as a single agent, is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

**r/m SCCHN**
OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

**mUC**
OPDIVO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**r/p cHL**
OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Ad/adjvant, ALK=anaplastic lymphoma kinase, aRCC=advanced RCC, EGFR=epidermal growth factor receptor, mMelanoma=metastatic melanoma, mNSCLC=metastatic NSCLC, mUC=metastatic urothelial carcinoma, r/m=recurrent or metastatic, r/p=relapsed or progressed, tx=treatment.

**SELECT IMPORTANT SAFETY INFORMATION**

**Infusion-Related Reactions**
OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Intermittent or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY® (ipilimumab) on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
**OPDIVO® monotherapy indications**

**MSI-H/dMMR mCRC**
OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**HCC**
OPDIVO, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**HCC**
OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**aESCC**
OPDIVO is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

**Adj tx of resected EC or GEJC**
OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiation therapy (CRT).

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**SELECT IMPORTANT SAFETY INFORMATION**

**Infusion-Related Reactions**
OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Intermittent or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

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**GO TO DOSING**
**INDUCTION DOSING (OPDIVO® 1 mg/kg followed by YERVOY® 3 mg/kg q3w)**

**OPDIVO MAINTENANCE DOSING**

**CHOICE OF 2 FLAT-DOSING OPTIONS**

- q2w (240 mg)
- q4w (480 mg)

Treat until disease progression or unacceptable toxicity during induction or maintenance therapy.

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**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**

In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%), and to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%).

**Common Adverse Reactions**

- Diarrhea (62%), rash (53%), nausea (44%), pyrexia (40%), pruritus (33%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (27%), upper respiratory tract infection (23%), arthralgia (28%), and increased transaminases (3%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (53%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%).

- In a separate Phase 3 trial of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19-24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions
In Checkmate 040, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=154). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, pneumonia, and anemia. In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). The most frequent serious adverse reactions reported in ≥4% of patients receiving OPDIVO with YERVOY were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Common Adverse Reactions
In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY were rash (33%), pruritus (33%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (27%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

The first dose of OPDIVO monotherapy should be administered after completing 4 doses of the OPDIVO and YERVOY combination therapy.

Based on exploratory dose exposure response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.

Review the U.S. Full Prescribing Information for OPDIVO and YERVOY for recommended dosage information.

No premedication required with OPDIVO + YERVOY.
**OPDIVO MAINTENANCE DOSING**

**CHOICE OF 2 FLAT-DOSING OPTIONS**

- q2w (240 mg)
- q4w (480 mg)

Treat until disease progression or unacceptable toxicity during induction or maintenance therapy.

**INDUCTION DOSING (OPDIVO® 3 mg/kg followed by YERVOY® 1 mg/kg q3w)**

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<thead>
<tr>
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<tr>
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*For MSI-H/dMMR mCRC adult and pediatric patients age 12 years and older and weighing 40 kg or more, follow OPDIVO dosing above. For pediatric patients age 12 years and older and weighing less than 40 kg, OPDIVO induction dosing is the same as the above and maintenance dosing is 3 mg/kg every 2 weeks (30-minute IV infusion).

‡OPDIVO is administered as a 30-minute IV infusion in both the induction and maintenance phases.

‡YERVOY is administered as a 30-minute IV infusion.

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**

- In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration.

**Common Adverse Reactions**

- In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent (n=74), the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), pyrexia (26%), constipation (23%), rash (22%), decreased appetite (20%), and cough (16%).

- In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musclebone pain (36%), abdominal pain (35%), pyrexia (28%), nausea (25%), rash (22%), decreased appetite (20%), and vomiting (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
PD-L1 ≥1% mNSCLC

In certain patients with PD-L1 ≥1% mNSCLC

CONTINUOUS DOSING (OPDIVO® 3 mg/kg and YERVOY® 1 mg/kg)

Weeks 0 1 2 3 4 5 6 7 8 9 10 11 12

CONTINUE TREATMENT
OPDIVO 3 mg/kg q2w + YERVOY 1 mg/kg q6w
Treat until disease progression, unacceptable toxicity, or for up to 2 years

*OPDIVO is administered as an IV infusion over 30 minutes.
†YERVOY is administered as an IV infusion over 30 minutes.

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions
- In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea, colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure.

Common Adverse Reactions
- In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea, colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
INDUCTION DOSING (OPDIVO® 360 mg q3w + YERVOY® 1 mg/kg q6w + Pt-doublet chemo q3w)

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*OPDIVO is administered as an IV infusion over 30 minutes.
†YERVOY is administered as an IV infusion over 30 minutes.
‡Histology-based chemo; SQ patients: carboplatin AUC 6 + paclitaxel 200 mg/m² q3w; NSQ patients: carboplatin AUC 5 or 6 or cisplatin 75 mg/m² + pemetrexed 500 mg/m² q3w.

MAINTENANCE DOSING

OPDIVO 360 mg q3w + YERVOY 1 mg/kg q6w

Treat until disease progression, unacceptable toxicity, or for up to 2 years

No chemo maintenance required

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Common Adverse Reactions

In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19-24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
CONTINUOUS DOSING (OPDIVO® 360 mg and YERVOY® 1 mg/kg)

OPDIVO® + YERVOY

OPDIVO 360 mg q3w + YERVOY 1 mg/kg q6w

Treat until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis.

Common Adverse Reactions

In Checkmate 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY were fatigue (43%), musculoskeletal pain (38%), rash (34%), diarrhea (32%), dyspnea (27%), nausea (24%), decreased appetite (24%), cough (23%), and pruritus (21%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
**INDUCTION DOSING (OPDIVO® 3 mg/kg followed by YERVOY® 1 mg/kg q3w)**

- **OPDIVO**
  - Week 0: 3 mg/kg
  - Week 1: 3 mg/kg
  - Week 2: 3 mg/kg
  - Week 3: 3 mg/kg
  - Week 4: 3 mg/kg
  - Week 5: 3 mg/kg
  - Week 6: 3 mg/kg
  - Week 7: 3 mg/kg
  - Week 8: 3 mg/kg
  - Week 9: 3 mg/kg
  - Week 10: 3 mg/kg
  - Week 11: 3 mg/kg
  - Week 12: 3 mg/kg

- **YERVOY**
  - Week 0: 1 mg/kg
  - Week 1: 1 mg/kg
  - Week 2: 1 mg/kg
  - Week 3: 1 mg/kg
  - Week 4: 1 mg/kg
  - Week 5: 1 mg/kg
  - Week 6: 1 mg/kg
  - Week 7: 1 mg/kg
  - Week 8: 1 mg/kg
  - Week 9: 1 mg/kg
  - Week 10: 1 mg/kg
  - Week 11: 1 mg/kg
  - Week 12: 1 mg/kg

**OPDIVO MAINTENANCE DOSING**

**CHOICE OF 2 FLAT-DOSING OPTIONS**

- q2w (240 mg)
- q4w (480 mg)

Treat until disease progression or unacceptable toxicity during induction or maintenance therapy.

*OPDIVO is administered as a 30-minute IV infusion in both the induction and maintenance phases.*

†YERVOY is administered as a 30-minute IV infusion.

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**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**

- In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥1% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

**Common Adverse Reactions**

- In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
CABOMETYX® + OPDIVO®*

**CHOICE OF 2 DOSING OPTIONS**
- q2w (240 mg) or q4w (480 mg) IV*
- ONCE-Daily TABLET (40 mg)

*OPDIVO is administered as an IV infusion over 30 minutes.

**DOSING**

**ONCE-DAILY TABLET (40 mg)**
- (without food, until disease progression or unacceptable toxicity)

**CHOICE OF 2 DOSING OPTIONS**
- q2w (240 mg) or q4w (480 mg) IV*
- (until disease progression, unacceptable toxicity, or up to 2 years)

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**
- In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

**Common Adverse Reactions**
- In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (57%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%) and upper respiratory tract infection (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
Advanced or metastatic GC, GEJC, and EAC

In 1L patients

OPDIVO with fluoropyrimidine- and platinum-containing chemotherapy

OR

OPDIVO 240 mg q2w

OPDIVO 360 mg q3w

Continue treatment until disease progression, unacceptable toxicity, or up to 2 years

The recommended dose of OPDIVO is:

- 360 mg q3w (30-minute IV infusion) with fluoropyrimidine- and platinum-containing chemotherapy q3w, or
- 240 mg q2w (30-minute IV infusion) with fluoropyrimidine- and platinum-containing chemotherapy q2w
- Continue treatment until disease progression, unacceptable toxicity, or up to 2 years
- Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO for the recommended dosage and administration information, as appropriate
- Administer OPDIVO first followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- In Checkmate 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO 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%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO 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.

Common Adverse Reactions

- In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19-24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
OPDIVO® monotherapy indications

Adj tx of melanoma
OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

mMelanoma
OPDIVO, as a single agent, is indicated for the treatment of patients with unresectable or metastatic melanoma.

aRCC
OPDIVO, as a single agent, is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

mNSCLC
OPDIVO, as a single agent, is indicated for the treatment of 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.

mUC
OPDIVO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

r/m SCCHN
OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

r/p chL
OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions
- OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Intermittent or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.

In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. In addition, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
OPDIVO® monotherapy indications (cont’d)

**MSI-H/dMMR mCRC**
OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**HCC**
OPDIVO, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**aESCC**
OPDIVO is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

**Adj tx of resected EC or GEJC**
OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiation therapy (CRT).

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**SELECT IMPORTANT SAFETY INFORMATION**

**Infusion-Related Reactions**
OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.

In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY® (ipilimumab) on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
Dosing optimized by indication for your patients

**OPDIVO® monotherapy dosing**

- Based on exploratory dose exposure response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.
- Review the U.S. Full Prescribing Information for recommended dosage information for OPDIVO.
- No premedication required.

**SELECT IMPORTANT SAFETY INFORMATION**

### Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Intermittent or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.

In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.
Adjacent resected EC or GEJC with residual pathologic disease following neoadjuvant CRT

- **Choice of 2 dosing options**
  - q2w (240 mg)
  - q4w (480 mg)

- **Until disease progression or unacceptable toxicity**
- **for a total treatment duration of 1 year**

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**
- In Checkmate 577, serious adverse reactions occurred in 33% of patients receiving OPDIVO (n=532). A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal reaction of myocardial infarction occurred in one patient who received OPDIVO.

**Common Adverse Reactions**
- In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=532) were fatigue (34%), diarrhea (34%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

- OPDIVO® is administered over 30 minutes as an intravenous infusion.
- Based on exploratory dose exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.

Adj=adjvant; CRT=chemoradiation therapy; EC=esophageal cancer; GEJC=gastroesophageal junction cancer; q2w=every 2 weeks; q4w=every 4 weeks; tx=treatment.
Important Safety Information

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO® or YERVOY®. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. 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 and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, 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 and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3% (61/1994) of patients, including Grade 4 (0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 10% (5/49) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3% (266/8661) of patients, including Grade 4 (0.4%), Grade 3 (2.6%), and Grade 2 (2.6%). In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 5% (50/974) of patients, including Grade 4 (0.5%), Grade 3 (3.7%), and Grade 2 (0.7%). (continued on next page)
Important Safety Information (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Immune-Mediated Endocrinopathies (cont’d)

- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 3% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.9%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 2% (22/1266) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 4 (2.5%).

- In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.9%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 2% (22/1266) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 4 (2.5%).

- In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, diabetes occurred in 2.7% (56/1994) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

- In a separate Phase 3 trial of YERVOY 3 mg/kg monotherapy, Grade 2-5 immune-mediated endocrinopathies occurred in 4% (21/510) of patients. Severe to life-threatening (Grade 3-4) endocrinopathies occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate (Grade 2) endocrinopathy occurred in 12 patients (2.3%), including hypothyroidism, adrenal insufficiency, hypopituitarism, hypothyroidism and Cushing’s syndrome.

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO and YERVOY can cause immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (0.6%), Grade 3 (0.5%), and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

Immune-Mediated Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

- In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (0.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/451) of patients, including Grade 3 (4.8%) and Grade 2 (10%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.3%) and Grade 2 (4.2%).

- In a separate Phase 3 trial of YERVOY 3 mg/kg monotherapy, immune-mediated rash occurred in 15% (76/510) of patients, including Grade 3-5 (2.5%) and Grade 2 (12%).

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of c <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY 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/isoscular: myocarditis, pericarditis, vasculitis; nervous system: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myastheria gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; ocular: uveitis, iritis, and other ocular inflammatory toxicities can occur; 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 rheumatica; endocrine: hypoparathyroidism, other (hematologic/immune): hemolytic anemia, aplastic anemia, hermaphroditic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

(continued on next page)
Important Safety Information (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Other Immune-Mediated Adverse Reactions (cont’d)

- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY™ monotherapy or in combination with OPDIVO®, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: nervous system: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; cardiovascular: angioedema, temporal arteritis; ocular: blepharitis, episcleritis, orbital myositis, scleritis; gastrointestinal: pancreatitis (1.3%); other (hematologic/immune): conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psychosis.

- Some ocular IMAR 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, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (72/1194) of patients. In separate trials in which patients received OPDIVO monotherapy as a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 4.2% (5/119) of patients. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

- In separate Phase 3 trials of YERVOY 3 mg/kg and 10 mg/kg monotherapy, infusion-related reactions occurred in 2.9% (28/982) of patients.
Serious Adverse Reactions (cont’d)

receiving OPDIVO were gamma-glutamyltransferase increase (3.3%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dose delays (38% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (>10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=376). The most frequent (≥2%) serious adverse reactions were pneumonia, diarhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 3L, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspepsia, pyrexia, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspepsia, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 057, fatal adverse reactions occurred; these included events of infection (7 patients, including one case of Pneumocystis jiroveci pneumonia), pulmonary embolism (4 patients), and limbic encephalitis (1 patient). In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarhea, pneumonitis, pleural effusion, dyspepsia, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.7%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis. In Checkmate 214, serious adverse reactions occurred in 53% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diabetes, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspepsia, adrenal insufficiency, and colitis. In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diabetes, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hypotension. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarhea, small intestine obstruction, and general physical health deterioration. In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=178), serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 045, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=154). The most frequent serious adverse reactions reported in ≥2% of patients were pyrexia, astesic, back pain, general physical health deterioration, abdominal pain, pneumonitis, and anemia. In Checkmate 045, serious adverse reactions occurred in 59% of patients receiving OPDIVO (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diabetes, pneumonitis, acute kidney injury, musculoskeletal pain, dyspepsia, and respiratory failure. In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). Grade 3 or 4 adverse reactions reported in ≥2% of OPDIVO-treated patients included pneumonitis (9 patients, including one case of Pneumocystis jiroveci pneumonia), renal failure (6 patients), and lymphocytic interstitial pneumonitis (5 patients). In Checkmate 277, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY (n=492). Serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis. In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). Grade 3 or 4 adverse reactions reported in ≥2% of OPDIVO-treated patients included pneumonia (25%, 19, 15, and 11 patients, respectively), pneumonitis (4 patients), febrile neutropenia (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation. (continued on next page)
Important Safety Information (cont’d)

Common Adverse Reactions

- In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 068, the most common adverse reactions (≥20%) reported with OPDIVO (n=205) were dacearbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%) and pruritus (23% vs 14%). In Checkmate 067, the most common adverse reactions in the OPDIVO® plus YERVOY® arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common adverse reactions in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY® were fatigue (43%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (31%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY® were fatigue (43%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (31%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 9LA, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diabetes/collitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diabetes/collitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%).

- In Checkmate 067, the most common (≥20%) adverse reactions in patients treated with OPDIVO plus nivolumab (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), diarrhea (20%), vomiting (20%). In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), musculoskeletal pain (39%), decreased appetite (28%), constipation (27%), vomiting (26%), and diarrhea (25%). In Checkmate 066, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/collitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 067 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=205) were rash (22%) and decreased appetite (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=209) were rash (22%) and decreased appetite (21%). In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=532) were fatigue (34%), diarrhea (29%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%). In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=1,122) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), arthralgia (39%), vomiting (37%), decreased appetite (29%), diarrhea (27%), constipation (25%), and musculoskeletal pain (20%).

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 19–24 and U.S. Full Prescribing Information for OPDIVO and YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

(continued on next page)
Clinical Trials and Patient Populations

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<tr>
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<td>Checkmate 645</td>
<td>previously untreated advanced or metastatic gastric, or gastroesophageal junction or esophageal adenocarcinoma</td>
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Please see full indications on pages 2–5, additional Important Safety Information for OPDIVO and YERVOY on pages 19–24, and U.S. Full Prescribing Information for OPDIVO and YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.