Please see Important Safety Information for OPDIVO® and YERVOY® (ipilimumab) on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
OPDIVO®

OPDIVO 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.1

YERVOY®

YERVOY is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response.2

OPDIVO + YERVOY combination therapy

Combined OPDIVO and YERVOY mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor response in metastatic melanoma, HCC, advanced RCC, and MSI-H/dMMR metastatic CRC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.1 During treatment with OPDIVO or OPDIVO + YERVOY, targeting of normal cells can also occur.3,4

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests, at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Purpose of this guide

Because of the importance of patient safety, we are providing this guide, which includes information on the incidence, recognition, and management of IMARs that may occur with OPDIVO® monotherapy and OPDIVO in combination with YERVOY®. IMARs may appear similar to side effects of chemotherapy, but they may need to be managed differently.5-11

Early identification and management of IMARs are essential to ensure safe and appropriate use of OPDIVO and OPDIVO with YERVOY. Upfront education regarding IMARs may increase confidence in IMAR management and support HCP/patient discussion, which may contribute to a more positive treatment experience for the patient.1,12

Additional resources

OPDIVO Safety Tool
A quick reference for the IMARs associated with OPDIVO treatment. You may access this app from your cellular phone, tablet, or computer. You can access the tool directly at OPDIVOsafetytool.com.
OPDIVO® is approved in 9 tumor types1

OPDIVO, as a single agent or in combination with YERVOY®, is indicated for the treatment of patients with unresectable or metastatic 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.

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

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 NSCLC, with no EGFR or ALK genomic tumor aberrations.

OPDIVO 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.

OPDIVO is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy. 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.

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

OPDIVO in combination with YERVOY, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced RCC.

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

Summary of Warnings and Precautions

- OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; 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 YERVOY on pages 42-45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
OPDIVO® is approved in 9 tumor types¹

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 a platinum-based therapy.

OPDIVO is indicated for treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 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.

OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric (12 years and older) patients 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.

OPDIVO, in combination with YERVOY®, is indicated for the treatment of adults 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. These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Considerations when managing immune-mediated adverse reactions\textsuperscript{1,5-12}

- Early recognition of potential IMARs
- Close monitoring of signs/symptoms
- Withholding or discontinuing therapy, use/taper of corticosteroids

While some side effects of immunotherapy may appear similar to chemotherapy, they may need to be managed differently.

Prompt patient reporting of side effects may help lead to identification of IMARs. While some patients may have to discontinue therapy, others may need to withhold therapy and may be able to resume after appropriate intervention and IMAR resolution.

For additional information, refer to the OPDIVO® US Prescribing Information and the OPDIVO Immune-Mediated Adverse Reactions Management Guide.

IMAR=immune-mediated adverse reaction.
Potential IMARs: signs and symptoms

**NEUROLOGIC**
- Headache
- Fever
- Tiredness
- Weakness
- Confusion
- Memory problems
- Sleepiness
- Seeing or hearing things that are not really there (hallucinations)
- Seizures
- Stiff neck

**ENDOCRINOPATHIES**
- Headaches that will not go away or unusual headaches
- Extreme tiredness
- Weight gain or weight loss
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Hair loss
- Feeling cold
- Constipation
- Voice gets deeper
- Excessive thirst or lots of urine
- Hypothyroidism

**HEPATITIS**
- Transaminase elevation
- Total bilirubin elevation
- Yellowing of the skin or the whites of the eyes
- Severe nausea or vomiting
- Pain on the right side of the stomach area (abdomen)
- Drowsiness
- Dark urine (tea colored)
- Bleeding or bruising more easily than normal
- Feeling less hungry than usual
- Decreased energy

**MYOCARDITIS***
- Cardio-pulmonary and cardiac symptoms; potential signs and symptoms may include:
  - Chest pain
  - Shortness of breath
  - Fatigue
  - Palpitations
  - Syncope

**PNEUMONITIS**
- Radiographic changes
- New or worsening cough
- Chest pain
- Shortness of breath

**NEPHRITIS AND RENAL DYSFUNCTION**
- Increase in serum creatinine
- Decrease in the amount of urine
- Blood in urine
- Swelling in ankles
- Loss of appetite

**SKIN ADVERSE REACTIONS**
- Rash
- Itching
- Skin blistering
- Ulcers in mouth or other mucous membranes

**SEVERE INFUSION-RELATED REACTIONS**
- Chills or shaking
- Itching or rash
- Flushing
- Difficulty breathing
- Dizziness
- Fever
- Feeling like passing out

**COLITIS**
- Diarrhea (loose stools) or more bowel movements than usual
- Blood in stools or dark, tarry, sticky stools
- Severe stomach-area (abdomen) pain or tenderness

**PROBLEMS IN OTHER ORGANS**
- Changes in eyesight
- Severe or persistent muscle or joint pains
- Severe muscle weakness
- Chest pain
- Upper respiratory tract infection

**Hepatitis**
- Transaminase elevation
- Total bilirubin elevation
- Yellowing of the skin or the whites of the eyes
- Severe nausea or vomiting
- Pain on the right side of the stomach area (abdomen)
- Drowsiness
- Dark urine (tea colored)
- Bleeding or bruising more easily than normal
- Feeling less hungry than usual
- Decreased energy

These are not all the possible organ systems that may be affected.

Additional signs and symptoms associated with YERVOY® include eye pain or redness, skin blistering or peeling, numbness or tingling in hands or feet, and unusual weakness of legs, arms, or face.

The most common side effects of OPDIVO® when used in combination with YERVOY are bolded above.

*Diagnosis of myocarditis requires a high index of suspicion, and in some cases can be asymptomatic.
IMAR=immune-mediated adverse reaction.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Routine monitoring tests for potential IMARs\textsuperscript{1,2}

- Educate and monitor patients for signs and symptoms of potential IMARs prior to and during treatment with OPDIVO\textsuperscript{®} or OPDIVO + YERVOY\textsuperscript{®}
  - IMARs can also manifest after discontinuation of therapy
- Patients should also be monitored for signs and symptoms of other adverse reactions, including infusion-related reactions and complications of allogeneic hematopoietic stem cell transplantation
- The following tables include recommended diagnostic and laboratory tests to monitor specific IMARs for patients receiving OPDIVO and OPDIVO + YERVOY
  - These recommended diagnostic and laboratory tests may also aid in monitoring for other IMARs

### Monitoring for OPDIVO as a single agent

Patients treated with OPDIVO as a single agent should be monitored prior to and periodically during treatment.

<table>
<thead>
<tr>
<th>IMAR</th>
<th>Recommended monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Radiographic imaging</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Liver function</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Thyroid function</td>
</tr>
<tr>
<td>- Hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Nephritis and renal dysfunction</td>
<td>Serum creatinine</td>
</tr>
</tbody>
</table>

### Monitoring for OPDIVO + YERVOY

Patients treated with OPDIVO + YERVOY should be monitored for the following values at baseline, before each dose, and as clinically indicated based on symptoms.

<table>
<thead>
<tr>
<th>IMAR</th>
<th>Recommended monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Radiographic imaging</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Liver function</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Adrenocorticotropic hormone levels</td>
</tr>
<tr>
<td>- Thyroid function</td>
<td></td>
</tr>
<tr>
<td>- Hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Nephritis and renal dysfunction</td>
<td>Serum creatinine</td>
</tr>
</tbody>
</table>

- This is not an exhaustive list of clinical tests and exams
- Monitor closely for symptoms and signs of underlying IMARs

IMAR=immune-mediated adverse reaction.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Recommended dose modifications for adverse reactions

- No dose reduction for **OPDIVO**® or **YERVOY**® is recommended.
- Recommendations for **OPDIVO** modifications are provided in the table below. When **OPDIVO** is administered in combination with **YERVOY**, if **OPDIVO** is withheld, **YERVOY** should also be withheld. Review the Prescribing Information for **YERVOY** for recommended dose modifications.
- There are no recommended dose modifications for hypothyroidism or hyperthyroidism.
- Discontinue **OPDIVO** in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions.

#### Table: Recommended dose modifications for adverse reactions

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Severity*</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 diarrhea or colitis</td>
<td>Withhold dose†</td>
<td></td>
</tr>
<tr>
<td>Grade 3 diarrhea or colitis</td>
<td>Withhold dose† when administered as a single agent</td>
<td></td>
</tr>
<tr>
<td>Grade 4 diarrhea or colitis</td>
<td>Permanently discontinue when administered with ipilimumab</td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 pneumonitis</td>
<td>Withhold dose†</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 pneumonitis</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis/ non-HCC</strong></td>
<td>Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis/HCC</strong></td>
<td>If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the baseline ULN</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Hypophysitis</strong></td>
<td>Grade 2 or 3 hypophysitis</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Grade 4 hypophysitis</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Adrenal insufficiency</strong></td>
<td>Grade 2 adrenal insufficiency</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Grade 3 or 4 adrenal insufficiency</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Type 1 diabetes mellitus</strong></td>
<td>Grade 3 hyperglycemia</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Grade 4 hyperglycemia</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Nephritis and renal dysfunction</strong></td>
<td>Serum creatinine more than 1.5 and up to 6 times the ULN</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Serum creatinine more than 6 times the ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Grade 4 rash or confirmed SJS or TEN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Encephalitis</strong></td>
<td>New-onset moderate or severe neurologic signs or symptoms</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Immune-mediated encephalitis</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td><strong>Other Grade 3 adverse reaction</strong></td>
<td>First occurrence</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>Recurrence of same Grade 3 adverse reaction</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Life-threatening or Grade 4 adverse reaction</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Grade 3 myocarditis</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
</tbody>
</table>

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).*

†Resume treatment when adverse reaction improves to Grade 0 or 1.

‡Resume treatment when AST/ALT returns to baseline.

Please see Important Safety Information for **OPDIVO** and **YERVOY** on pages 42–45 and US Full Prescribing Information for **OPDIVO** and **YERVOY**, including **Boxed WARNING** regarding immune-mediated adverse reactions for **YERVOY**. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
**OPDIVO® as a single agent**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended OPDIVO dosage</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic melanoma</td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>Until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td>Metastatic non-small cell lung cancer</td>
<td>480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td>Advanced renal cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of the head and neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>Until disease recurrence or unacceptable toxicity for up to 1 year</td>
</tr>
<tr>
<td>Adjuvant treatment of melanoma</td>
<td>480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>Until disease progression or unacceptable toxicity</td>
</tr>
</tbody>
</table>

No premedication required.

**OPDIVO in combination with YERVOY®**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended OPDIVO dosage</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic non-small cell lung cancer expressing PD-L1 ≥1%</td>
<td>3 mg/kg for 2 weeks (30-minute intravenous infusion) with YERVOY 1 mg/kg every 6 weeks (30-minute intravenous infusion)</td>
<td>In combination with YERVOY until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression</td>
</tr>
</tbody>
</table>

**Select Important Safety Information**

**Infusion-Related Reactions**

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. 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% (10/407) of patients. In RCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, 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 MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
OPDIVO® in combination with YERVOY® (cont’d)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended OPDIVO dosage</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unresectable or metastatic melanoma</strong></td>
<td>1 mg/kg every 3 weeks (30-minute intravenous infusion) with YERVOY 3 mg/kg intravenously</td>
<td>In combination with YERVOY for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier</td>
</tr>
<tr>
<td></td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>or 480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td>1 mg/kg every 3 weeks (30-minute intravenous infusion) with YERVOY 3 mg/kg intravenously</td>
<td>In combination with YERVOY for 4 doses</td>
</tr>
<tr>
<td></td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>or 480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td><strong>Advanced renal cell carcinoma</strong></td>
<td>3 mg/kg every 3 weeks (30-minute intravenous infusion) with YERVOY 1 mg/kg intravenously</td>
<td>In combination with YERVOY for 4 doses</td>
</tr>
<tr>
<td></td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>or 480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td><strong>Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer</strong></td>
<td>3 mg/kg every 3 weeks (30-minute intravenous infusion) with YERVOY 1 mg/kg intravenously</td>
<td>In combination with YERVOY for 4 doses</td>
</tr>
<tr>
<td>Adult patients and pediatric patients age 12 years and older and weighing</td>
<td>Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more:</td>
<td>After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td>40 kg or more: 240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td>240 mg every 2 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td>or 480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td>480 mg every 4 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
<tr>
<td>Pediatric patients age 12 years and older and weighing less than 40 kg:</td>
<td>Pediatric patients age 12 years and older and weighing less than 40 kg:</td>
<td></td>
</tr>
<tr>
<td>3 mg/kg every 2 weeks (30-minute intravenous infusion)</td>
<td>3 mg/kg every 2 weeks (30-minute intravenous infusion)</td>
<td></td>
</tr>
</tbody>
</table>

No premedication required.

Refer to the YERVOY Prescribing Information for recommended YERVOY dosage information.

aHCC=advanced hepatocellular carcinoma; ALT=alanine aminotransferase; aRCC=advanced renal cell carcinoma; AST=aspartate aminotransferase; CRC=colorectal cancer; dMMR=mismatch repair deficient; DRESS=drug rash with eosinophilia and systemic symptoms; IMAR=immune-mediated adverse reaction; mMelanoma=metastatic melanoma; MSI-H=microsatellite instability-high; mNSCLC=metastatic non-small cell lung cancer; mSCLC=metastatic small cell lung cancer; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis; ULN=upper limit of normal.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Summary of immune-mediated adverse reactions with OPDIVO® as a single agent

- Clinically significant adverse reactions of OPDIVO as a single agent were evaluated in 1994 patients enrolled in Checkmate 037, 017, 057, 066, 025, 067, 205, and 039, or a single-arm trial in NSCLC (n=117).†
- OPDIVO can cause severe infusion-related reactions, which have been reported in less than 1.0% of patients in clinical trials.†
- Please see pages 22–41 for respective management of immune-mediated adverse reactions in patients treated with OPDIVO.

Incidence and onset of immune-mediated adverse reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence, all grades, n (%)</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis*</td>
<td>61 (3.1)</td>
<td>range: 1 day to 22.3 months</td>
</tr>
<tr>
<td>Colitis</td>
<td>58 (2.9)</td>
<td>range: 2 days to 20.9 months</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>35 (1.8)</td>
<td>range: 6 days to 9 months</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>12 (0.6)</td>
<td>range: 1.4 to 11 months</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>20 (1)</td>
<td>range: 15 days to 21 months</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>171 (9)</td>
<td>range: 1 day to 16.6 months</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>54 (2.7)</td>
<td>range: 1 day to 14.2 months</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>17 (0.9)</td>
<td>range: 15 days to 22 months</td>
</tr>
<tr>
<td>Nephritis/renal dysfunction</td>
<td>23 (1.2)</td>
<td>range: 23 days to 12.3 months</td>
</tr>
<tr>
<td>Skin†</td>
<td>171 (9)</td>
<td>range: &lt;1 day to 25.8 months</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>3 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Fatal cases have been reported.† Two cases of diabetic ketoacidosis occurred.‡ OPDIVO can cause skin immune-mediated adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); some cases have fatal outcome.§ Fatal limbic encephalitis occurred in 1 patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. In the other 2 patients, encephalitis occurred post-allogeneic hematopoietic stem cell transplantation.†

NSCLC=non-small cell lung cancer.

Incidence and onset of infusion-related reactions/hypersensitivity

- In patients who received OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients.
- In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received OPDIVO as a 60-minute intravenous infusion or a 30-minute intravenous 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.

Select Important Safety Information

Other Immune-Mediated Adverse Reactions

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY®, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.
- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Summary of immune-mediated adverse reactions management and outcomes with OPDIVO® as a single agent

Clinically significant adverse reactions of OPDIVO as a single agent were evaluated in 1994 patients enrolled in Checkmate 037, 017, 057, 066, 025, 067, 205, and 039, or a single-arm trial in NSCLC (n=117).1

<table>
<thead>
<tr>
<th>Event (incidence; n)</th>
<th>Permanently discontinued OPDIVO (%)</th>
<th>Withheld OPDIVO (%)</th>
<th>Corticosteroid use</th>
<th>Other treatments</th>
<th>Resolution* (%)</th>
<th>Recurrence after re-initiation of OPDIVO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>Median duration (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis (3.1%; n=61)</td>
<td>1.1</td>
<td>1.3</td>
<td>26 days (1 day to 6 months)</td>
<td></td>
<td>57†</td>
<td>~8</td>
</tr>
<tr>
<td>Colitis (2.9%; n=58)</td>
<td>0.7</td>
<td>1</td>
<td>23 days (1 day to 9.3 months)</td>
<td>4 patients received infliximab in addition to high-dose CS</td>
<td>74†</td>
<td>~16</td>
</tr>
<tr>
<td>Hepatitis (1.8%; n=35)</td>
<td>0.7</td>
<td>1</td>
<td>23 days (1 day to 2 months)</td>
<td>2 patients received mycophenolic acid in addition to high-dose CS</td>
<td>74†</td>
<td>~29</td>
</tr>
<tr>
<td><strong>Endocrinopathies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis (0.6%; n=12)</td>
<td>0.1</td>
<td>0.2</td>
<td>14 days (5 to 26 days)</td>
<td>~67% received HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency (1%; n=20)</td>
<td>0.1</td>
<td>0.5</td>
<td>11 days (1 day to 1 month)</td>
<td>~85% received HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism/ thyroiditis (9%; n=171)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism (2.7%; n=54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes mellitus (0.9%; n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis, renal dysfunction (1.2%; n=23)</td>
<td>0.3</td>
<td>0.8</td>
<td>21 days (1 day to 15.4 months)</td>
<td></td>
<td>48†</td>
<td>0</td>
</tr>
<tr>
<td>Skin (9%; n=171)</td>
<td>0.3</td>
<td>0.8</td>
<td>12 days (1 day to 8.9 months)</td>
<td>85% received topical CS</td>
<td>48†</td>
<td>1.4</td>
</tr>
<tr>
<td>Encephalitis (0.2%; n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Resolution defined in the context of the IMAE time-to-resolution analyses; resolution date was defined as the investigator-assessed IMAE resolution date. In the analyses of complete resolution, complete resolution was defined as improved to Grade 0 or baseline grade per investigator assessment with completion of corticosteroid treatment (or other medical intervention).17 †At least 40 mg prednisone equivalents per day.1 Complete resolution following CS taper.1 Complete resolution following CS use.1

CS=corticosteroid; HRT=hormone replacement therapy; IMAE=immune-mediated adverse event; NSCLC=non-small cell lung cancer.

Please see Important Safety Information for OPDIVO and YERVYO® on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVYO, including Boxed WARNING regarding immune-mediated adverse reactions for YERVYO. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Summary of immune-mediated adverse reactions with OPDIVO® + YERVOY® in patients with mMelanoma

In patients with metastatic melanoma

- Clinically significant adverse reactions of OPDIVO in combination with YERVOY were evaluated in 407 patients with melanoma enrolled in Checkmate 067 (n=313) or a phase 2 randomized trial (n=94), administering OPDIVO with YERVOY.
- Please see pages 22–41 for respective management of immune-mediated adverse reactions in patients treated with OPDIVO + YERVOY.

Incidence and onset of immune-mediated adverse reactions1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence, n (%)</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>25 (6)</td>
<td>range: 24 days to 10.1 months</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>107 (26)</td>
<td>range: 3 days to 15.2 months</td>
</tr>
<tr>
<td>Hepatitis, including liver function test elevations</td>
<td>51 (13)</td>
<td>range: 15 days to 11 months</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>36 (9)</td>
<td>range: 27 days to 5.5 months</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>21 (5)</td>
<td>range: 21 days to 9.4 months</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>89 (22)</td>
<td>range: 1 day to 10.1 months</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>34 (8)</td>
<td>range: 3 days to 3.7 months</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>6 (1.5)</td>
<td>range: 1.3 to 4.4 months</td>
</tr>
<tr>
<td>Nephritis/renal dysfunction</td>
<td>9 (2.2)</td>
<td>range: 9 days to 7.9 months</td>
</tr>
<tr>
<td>Rash</td>
<td>92 (22.6)</td>
<td>range: 1 day to 9.7 months</td>
</tr>
<tr>
<td>Encephalitis†</td>
<td>1 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*After completing 4 doses of the combination, the recommended dose of OPDIVO in the single-agent phase is either 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.† Encephalitis occurred in 1 patient receiving OPDIVO + YERVOY (0.2%) after 1.7 months of exposure.

mMelanoma=metastatic melanoma; q2w=every 2 weeks; q3w=every 3 weeks.

Incidence and onset of infusion-related reactions/hypersensitivity1

Infusion-related reactions occurred in 2.5% (10/407) of patients.

Select Important Safety Information

Other Immune-Mediated Adverse Reactions

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.
- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
**Summary of immune-mediated adverse reactions management and outcomes with OPDIVO® + YERVOY® in mMelanoma**

**In patients with metastatic melanoma**

Clinically significant adverse reactions of OPDIVO in combination with YERVOY (OPDIVO 1 mg/kg followed by YERVOY 3 mg/kg every 3 weeks for 4 doses, then OPDIVO 240 mg every 2 weeks) were evaluated in 407 patients with melanoma enrolled in Checkmate 067 (n=313) or a phase 2 randomized trial (n=94), administering OPDIVO with YERVOY.1,30-32

<table>
<thead>
<tr>
<th>Event (incidence; n)</th>
<th>Permanently discontinued OPDIVO with YERVOY (%)</th>
<th>Withheld OPDIVO with YERVOY (%)</th>
<th>Corticosteroid use</th>
<th>Other treatments</th>
<th>Resolution (%)*</th>
<th>Recurrence after re-initiation of OPDIVO with YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (6%; n=25)</td>
<td>2.2</td>
<td>3.7</td>
<td>~84†</td>
<td>30 days (5 days to 11.8 months)</td>
<td>–</td>
<td>68†</td>
</tr>
<tr>
<td>Diarrhea/colitis (25%; n=107)*</td>
<td>15.7</td>
<td>7.3</td>
<td>~96†</td>
<td>1.1 months (1 day to 12 months)</td>
<td>~23% received infliximab in addition to high-dose CS</td>
<td>75†</td>
</tr>
<tr>
<td>Hepatitis (13%; n=51)</td>
<td>6.4</td>
<td>5.2</td>
<td>~92†</td>
<td>1.2 months (1 day to 13.2 months)</td>
<td>–</td>
<td>75†</td>
</tr>
</tbody>
</table>

**Endocrinopathies**

| Hypophysitis (9%; n=36) | 1 | 3.9 | 56† | 19 days (1 day to 2.0 months) | – | – | – |
| Adrenal insufficiency (5%; n=21) | 0.5 | 1.7 | 33† | 9 days (1 day to 2.7 months) | – | – | – |
| Hypothyroidism/thyroiditis (22%; n=85) | 1.5 | 2.7 | 7† | 0.9 months or 27 days (19 days to 1.6 months) | ~73% received levothyroxine | 45 | – |
| Hyperthyroidism (8%; n=34) | 0 | 3.2 | 15† | 23 days (5 to 29 days) | ~29% received methimazole; ~24% received carbimazole | 94 | – |
| Type 1 diabetes mellitus (1.5%; n=6) | 1 patient | 1 patient | – | – | – | – | – |
| Nephritis, renal dysfunction (2.2%; n=9) | 0.7 | 0.5 | ~61† | 13.5 days (1 day to 1.3 months) | – | 100† | 0† |
| Rash (22.6%; n=92) | 0.5 | 3.9 | ~17† | 14 days (2 days to 4.7 months) | – | 47† | 3 patients |
| Encephalitis (0.2%; n=1) | – | – | – | – | – | – | – |

*Resolution defined in the context of the IMAE time-to-resolution analyses; resolution date was defined as the investigator-assessed IMAE resolution date. In the analyses of complete resolution, complete resolution was defined as improved to Grade 0 or baseline grade per investigator assessment with completion of CS treatment (or other medical intervention).1 At least 40 mg prednisone equivalents per day.1 Complete resolution following CS use.1

Includes 3 fatal cases.1 Two patients resumed OPDIVO with YERVOY without recurrence of nephritis or renal dysfunction.1

CS=corticosteroid; HRT=hormone replacement therapy; IMAE=immune-mediated adverse event; mMelanoma=metastatic melanoma.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Summary of immune-mediated adverse reactions with OPDIVO® + YERVOY® in patients with HCC

In patients with hepatocellular carcinoma who have been previously treated with sorafenib
- Clinically significant adverse reactions of OPDIVO in combination with YERVOY were evaluated in 49 previously treated patients with HCC enrolled in Checkmate 040.1
- Please see pages 22–41 for respective management of immune-mediated adverse reactions in patients treated with OPDIVO + YERVOY

Incidence and onset of immune-mediated adverse reactions1,18

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence, all grades, n (%)</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis†</td>
<td>5 (10)</td>
<td>range: 1.2 to 17.5 months</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>5 (10)</td>
<td>range: 1.1 to 19 months</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>10 (20)</td>
<td>range: 22 days to 4.1 months</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>2 (4)</td>
<td>range: 3 to 4.3 months</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>9 (18)</td>
<td>range: 1.4 to 8 months</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>11 (22)</td>
<td>range: 1.4 to 16.2 months</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>5 (10)</td>
<td>range: 1.4 to 2.8 months</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nephritis/renal dysfunction</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash‡</td>
<td>17 (35)</td>
<td>range: 6 days to 3.1 months</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*After completing 4 doses of the combination, the recommended dose of OPDIVO in the single-agent phase is either 240 mg every 2 weeks, or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. Fatal cases have been reported. OPDIVO can cause skin immune-mediated adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome.

HCC = hepatocellular carcinoma; q2w = every 2 weeks; q3w = every 3 weeks.

Incidence and onset of infusion-related reactions/hypersensitivity

Infusion-related reactions occurred in 8% (4/49) of patients. Median time to onset was 10.3 weeks (range: 0.1–21.1 weeks).19

Select Important Safety Information

Other Immune-Mediated Adverse Reactions
- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Summary of immune-mediated adverse reactions management and outcomes with OPDIVO® + YERVOY® in HCC

In patients with hepatocellular carcinoma who have been previously treated with sorafenib

Clinically significant adverse reactions of OPDIVO in combination with YERVOY (OPDIVO 1 mg/kg followed by YERVOY 3 mg/kg every 3 weeks for 4 doses, then OPDIVO 240 mg every 2 weeks) were evaluated in 49 patients with hepatocellular carcinoma enrolled in Checkmate 040.1,2,18,29

<table>
<thead>
<tr>
<th>Event (incidence; %)</th>
<th>Permanently discontinued OPDIVO with YERVOY (%)</th>
<th>Withheld OPDIVO with YERVOY (%)</th>
<th>Corticosteroid use (%)</th>
<th>Median duration (range)</th>
<th>Other treatments</th>
<th>Resolution (%)</th>
<th>Recurrence after re-initiation of OPDIVO with YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (10%; n=5)</td>
<td>6.1</td>
<td>4.1</td>
<td>100*</td>
<td>23 days (12 days to 1.4 months)</td>
<td>20% received infliximab</td>
<td>60†</td>
<td>0</td>
</tr>
<tr>
<td>Colitis (10%; n=5)</td>
<td>4.1</td>
<td>6.1</td>
<td>60†</td>
<td>15 days (9 days to 1.1 months)</td>
<td>20% received mycophenolic acid; 20% received infliximab</td>
<td>80†</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis (20%; n=10)</td>
<td>6.1</td>
<td>14.3</td>
<td>70†</td>
<td>14 days (3 days to 34 months)</td>
<td>–</td>
<td>70†</td>
<td>0</td>
</tr>
</tbody>
</table>

**Endocrinopathies**

<table>
<thead>
<tr>
<th>Event</th>
<th>Permanently discontinued OPDIVO with YERVOY (%)</th>
<th>Withheld OPDIVO with YERVOY (%)</th>
<th>Corticosteroid use (%)</th>
<th>Median duration (range)</th>
<th>Other treatments</th>
<th>Resolution (%)</th>
<th>Recurrence after re-initiation of OPDIVO with YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophysitis (4%; n=2)</td>
<td>0</td>
<td>2</td>
<td>50†</td>
<td>6 days</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency (18%; n=9)</td>
<td>0</td>
<td>4</td>
<td>11†</td>
<td>1.2 months</td>
<td>–</td>
<td>22†</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis (22%; n=11)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>91% received levothyroxine</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism (10%; n=5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus (0%; n=0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nephritis, renal dysfunction (0%; n=0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rash (35%; n=17)</td>
<td>0</td>
<td>6.1</td>
<td>12†</td>
<td>8 days (1 to 15 days)</td>
<td>5.9% received HCTOP/MICNTP</td>
<td>65†</td>
<td>0</td>
</tr>
<tr>
<td>Encephalitis (0%; n=0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Resolution was defined in the context of the IMAE time-to-resolution analyses; resolution date was defined as the investigator-assessed IMAE resolution date. In the analyses of complete resolution, complete resolution was defined as improved to Grade 0 or baseline grade per investigator assessment with completion of CS treatment (or other medical intervention).†‡ At least 40 mg prednisone equivalents per day.‡ Complete resolution following CS use.† CS=corticosteroid; HCC=hepatocellular carcinoma; IMAE=immune-mediated adverse event.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Summary of immune-mediated adverse reactions with OPDIVO® + YERVOY® in patients with aRCC

In patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma

- Clinically significant adverse reactions of OPDIVO in combination with YERVOY were evaluated in the first-line treatment of 547 patients with aRCC enrolled in Checkmate 214.
- Please see pages 22–41 for respective management of immune-mediated adverse reactions in patients treated with OPDIVO + YERVOY.

### Incidence and onset of immune-mediated adverse reactions

### Incidence and onset of immune-mediated adverse reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence, all grades, n (%)</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>24 (4.4)</td>
<td>range: 8 days to 9.2 months</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>52 (10)</td>
<td>range: 2 days to 19.2 months</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>38 (7)</td>
<td>range: 14 days to 26.8 months</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>25 (4.6)</td>
<td>range: 1.3 to 7.3 months</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>41 (7)</td>
<td>range: 2.0 to 22.3 months</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>119 (22)</td>
<td>range: 1 day to 21.4 months</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>66 (12)</td>
<td>range: 6 days to 14.2 months</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>15 (2.7)</td>
<td>range: 19 days to 16.8 months</td>
</tr>
<tr>
<td>Nephritis/renal dysfunction</td>
<td>25 (4.6)</td>
<td>range: 1 day to 13.2 months</td>
</tr>
<tr>
<td>Skin</td>
<td>90 (16)</td>
<td>range: 1 day to 20.9 months</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*After completing 4 doses of the combination, the recommended dose of OPDIVO in the single-agent phase is either 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.1 Fatal cases have been reported.1 OPDIVO can cause skin immune-mediated adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); some cases with fatal outcome.1

### Incidence and onset of infusion-related reactions

Infusion-related reactions occurred in 5.1% (28/547) of patients. Median time to onset not available.

### Select Important Safety Information

**Other Immune-Mediated Adverse Reactions**

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Summary of immune-mediated adverse reactions management and outcomes with OPDIVO® + YERVOY® in aRCC

In patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma

Clinically significant adverse reactions of OPDIVO in combination with YERVOY (OPDIVO 3 mg/kg followed by YERVOY 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks) were evaluated in the first-line treatment of 547 patients with aRCC enrolled in Checkmate 214.1,20-23

<table>
<thead>
<tr>
<th>Event (incidence; n)</th>
<th>Permanently discontinued OPDIVO with YERVOY (%)</th>
<th>Withheld OPDIVO with YERVOY (%)</th>
<th>Corticosteroid use</th>
<th>Other treatments</th>
<th>Resolution* (%)</th>
<th>Recurrence after re-initiation of OPDIVO with YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (4.4%; n=24)</td>
<td>2.0</td>
<td>1.6</td>
<td>-92†</td>
<td>19 days (4 days to 3.2 months)</td>
<td>~8% of patients received infliximab in addition to high-dose CS</td>
<td>79‡</td>
</tr>
<tr>
<td>Colitis (10%; n=52)</td>
<td>3.5</td>
<td>4.2</td>
<td>-83‡</td>
<td>21 days (1 day to 27 months)</td>
<td>~23% of patients received infliximab in addition to high-dose CS</td>
<td>89‡</td>
</tr>
<tr>
<td>Hepatitis (7%; n=38)</td>
<td>3.7</td>
<td>3.1</td>
<td>-92†</td>
<td>1 month (1 day to 4 months)</td>
<td>~16% received mycophenolic acid</td>
<td>87§</td>
</tr>
</tbody>
</table>

**Endocrinopathies**

| Hypophysitis (4.6%; n=25) | 0.9 | 2.0 | 60† | 10 days (1 day to 1.6 months) | 72% received HRT | 60 | – |
| Adrenal insufficiency (7%; n=41) | 1.3 | 2.2 | 22† | 12 days (2 days to 5.6 months) | ~93% received HRT | 24 | – |
| Hypothyroidism/ thyroiditis (22%; n=119) | 0.4 | 1.1 | ~9 | 22 days (12 days to 2.1 months) | ~81% received levothyroxine; ~10% received HRT | – | – |
| Hyperthyroidism (12%; n=66) | 0 | 1.5 | -18 | 15 days (1 day to 1.5 months) | ~23% received HRT | – | – |
| Type 1 diabetes mellitus (2.7%; n=15) | 0.2 | 0 | 0 | – | ~7% received HRT | 27 | – |
| Nephritis, renal dysfunction (4.6%; n=25) | 1.1 | 2.7 | -76† | 15 days (1 day to 5.9 months) | – | 64‡ | 1 patient |
| Skin (16%; n=90) | 0.5 | 2.9 | -19† | 25 days (1 day to 23.1 months) | – | 64‡ | – |
| Encephalitis (0.2%; n=1) | – | – | – | – | – | – | – |

*Resolution was defined in the context of the IMAE time-to-resolution analyses; the resolution date was defined as the investigator-assessed IMAE resolution date. In the analyses of complete resolution, complete resolution was defined as improved to Grade 0 or baseline grade per investigator assessment with completion of CS treatment (or other medical intervention). † At least 40 mg prednisone equivalents per day. ‡ Complete resolution following CS use. § aRCC=advanced renal cell carcinoma; CS=corticosteroid; HRT=hormone replacement therapy; IMAE=immune-mediated adverse event.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
In adult and pediatric patients 12 years and older with MSI-H/dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

- Clinically significant adverse reactions of OPDIVO in combination with YERVOY were evaluated in 119 patients with MSI-H or dMMR mCRC enrolled in Checkmate 142.
- Please see pages 22–41 for respective management of immune-mediated adverse reactions in patients treated with OPDIVO + YERVOY.

**Incidence and onset of immune-mediated adverse reactions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence, all grades, n (%)</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>2 (1.7)</td>
<td>range: 27 days to 3 months</td>
</tr>
<tr>
<td>Colitis</td>
<td>8 (6.7)</td>
<td>range: 22 days to 5.2 months</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>10 (8.4)</td>
<td>range: 22 days to 10.5 months</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>4 (3.4)</td>
<td>range: 2.8 to 5.5 months</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>7 (5.9)</td>
<td>range: 2.5 to 13.4 months</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>18 (15.1)</td>
<td>range: 22 days to 9.8 months</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14 (11.8)</td>
<td>range: 21 days to 5.4 months</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nephritis/renal dysfunction</td>
<td>2 (1.7)</td>
<td>range: 1.6 to 5.5 months</td>
</tr>
<tr>
<td>Skin†</td>
<td>17 (14.3)</td>
<td>range: 5 days to 9.8 months</td>
</tr>
<tr>
<td>Encephalitis‡</td>
<td>1 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

*After completing 4 doses of the combination, the recommended dose of OPDIVO for adult and pediatric patients age 12 years and older: weighing 40 kg or more is either 240 mg every 2 weeks or 480 mg every 4 weeks; weighing less than 40 kg is 3 mg/kg every 2 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.*

**Incidence and onset of infusion-related reactions/hypersensitivity**

Infusion-related reactions occurred in 4.2% (5/119) of patients, of which 3 (2.5%) required treatment with immune-modulating medication. Median time to onset was 2.1 months (range: 22 days to 12.2 months).

**Select Important Safety Information**

**Other Immune-Mediated Adverse Reactions**

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Summary of immune-mediated adverse reactions management and outcomes with OPDIVO® + YERVOY® in MSI-H/dMMR mCRC

In adult and pediatric patients 12 years and older with MSI-H/dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

Clinically significant adverse reactions of OPDIVO in combination with YERVOY (OPDIVO 3 mg/kg followed by YERVOY 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks) were evaluated in 119 patients with mCRC enrolled in Checkmate 142.

<table>
<thead>
<tr>
<th>Event (incidence; %)</th>
<th>Permanently discontinued OPDIVO with YERVOY (%)</th>
<th>Withheld OPDIVO with YERVOY (%)</th>
<th>Corticosteroid use</th>
<th>Median duration (range)</th>
<th>Other treatments</th>
<th>Resolution* (%)</th>
<th>Recurrence after re-initiation of OPDIVO with YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (1.7%; n=2)</td>
<td>1 patient</td>
<td>1.7</td>
<td>100(^1)</td>
<td>16 months (12 days to 2.8 months)</td>
<td>100% received HRT</td>
<td>100(^1)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Colitis (6.7%; n=8)</td>
<td>1.7</td>
<td>2.5</td>
<td>~63(^1)</td>
<td>22 days (14 days to 14 months)</td>
<td>25% of patients received infliximab in addition to high-dose CS</td>
<td>88(^1)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis (8.4%; n=10)</td>
<td>3.4</td>
<td>5.0</td>
<td>100(^1)</td>
<td>1.8 months (11 days to 7.5 months)</td>
<td>30% of patients received mycophenolic acid in addition to high-dose CS</td>
<td>70(^1)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Endocrinopathies**

| Hypophysitis (3.4%; n=4) | 1 patient | 2.5 | 25\(^1\) | 26 days in 1 patient | 75% received HRT | 50 | 0 |
| Adrenal insufficiency (5.9%; n=7) | 1 patient | 3.4 | 57\(^1\) | 11 days (2 days to 16 days) | 100% received HRT | 57 | 0 |
| Hypothyroidism/thyroiditis (15.1%; n=18) | 0 | 1.7 | 0 | – | 78% received levothyroxine | – | 0 |
| Hyperthyroidism (11.8%; n=14) | 0 | 2.5 | 7\(^1\) | 19 days in 1 patient | ~7% received HRT | – | 0 |
| Type 1 diabetes mellitus (0%; n=0) | – | – | – | – | – | – | – |
| Nephritis, renal dysfunction (1.7%; n=2) | 1.7 | 0 | 100\(^1\) | 17 months (1 month to 2.4 months) | – | 50\(^1\) | – |
| Skin (14.3%; n=17) | 0 | 1 patient | 18\(^1\) | 15 days (11 days to 23 days) | – | 71\(^1\) | 0 |
| Encephalitis (0.8%; n=1) | – | – | 100\(^1\) | – | 1 patient received infliximab in addition to high-dose CS | – | – |

\(^*\)Resolution was defined in the context of the IMAE time-to-resolution analyses; resolution date was defined as the investigator-assessed IMAE resolution date. In the analyses of complete resolution, complete resolution was defined as improved to Grade 0 or baseline grade per investigator assessment with completion of CS treatment (or other medical intervention).\(^1\) At least 40 mg prednisone equivalent per day.\(^\dagger\) Complete resolution following CS use.\(^1\)

CS=corticosteroid; dMMR=mismatch repair deficient; HRT=hormone replacement therapy; IMAE=immune-mediated adverse event; mCRC=metastatic colorectal cancer; MSI-H=microsatellite instability-high.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Signs, symptoms, and management of immune-mediated adverse reactions

This section contains guidance for the management of select immune-mediated adverse reactions, which includes adverse reaction management algorithms from the clinical trials of OPDIVO® and OPDIVO + YERVOY®.

For ease of use, this guidance is organized by body system and contains both management and follow-up information.

- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.
- Corticosteroids are a primary treatment for immunotherapy-related adverse events. The oral equivalent of the recommended intravenous doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
- The frequency and severity of the related adverse events covered by these algorithms will depend on the immunotherapeutic agent or regimen being used.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Please see Important Safety Information for OPDIVO® and YERVOY® on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Select Important Safety Information

Immune-Mediated Pneumonitis

- **OPDIVO®** can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY® 3 mg/kg, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) of patients. In NSCLC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 14% (79/576) of patients. The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with OPDIVO 360 mg every 3 weeks in combination with YERVOY 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with OPDIVO in combination with YERVOY only.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO. Grade 3 (n=1) and Grade 2 (n=12).

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Management of immune-mediated pulmonary adverse reactions

Immune-mediated pulmonary adverse reactions \(^{1,12,26}\)

When OPDIVO® is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Treatment with OPDIVO or OPDIVO + YERVOY</th>
<th>Monitoring</th>
<th>Consult</th>
<th>Steroids¹</th>
<th>Pulmonary tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue treatment</td>
<td>Every 2 to 3 days</td>
<td>Consider pulmonary and infectious disease</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Withhold dose¹</td>
<td>Daily</td>
<td>Pulmonary and infectious disease</td>
<td>1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month</td>
<td>Consider bronchoscopy, lung biopsy</td>
</tr>
<tr>
<td>Permanently discontinue</td>
<td>Hospitalize</td>
<td>Pulmonary and infectious disease</td>
<td>1 to 2 mg/kg/day prednisone equivalents⁵ followed by corticosteroid taper over at least 6 weeks</td>
<td>Consider bronchoscopy, lung biopsy</td>
</tr>
</tbody>
</table>

Follow-up \(^{1,12,18}\)

<table>
<thead>
<tr>
<th>Re-image at least every 3 weeks</th>
<th>Re-image every 1–3 days</th>
<th>If worsens</th>
<th>If not improving after 2 weeks or worsening</th>
<th>If persists or worsens after 2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Treat as Grade 2 or 3-4</td>
<td>• Treat as Grade 3-4</td>
<td>• Add non-corticosteroid immunosuppressive medication</td>
</tr>
</tbody>
</table>

In clinical trials, some patients with immune-mediated pneumonitis received treatments other than corticosteroids.

<table>
<thead>
<tr>
<th>OPDIVO as a single agent</th>
<th>OPDIVO + YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>In mMelanoma (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)</td>
<td>In HCC (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)</td>
</tr>
<tr>
<td>Other treatments for pneumonitis</td>
<td>–</td>
</tr>
</tbody>
</table>

*Grades correspond to those listed in the NCI CTCAE Version 4.0.\(^{1,26}\) *Resume treatment when adverse reaction returns to Grade 0 or 1.\(^{11}\) *Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at the start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.\(^{15}\) *Add prophylactic antibiotics for opportunistic infections.\(^{12}\) *Consider adding prophylactic antibiotics.\(^{12}\) aRCC=advanced renal cell carcinoma; CS=corticosteroids; dMMR=mismatch repair deficient; HCC=hepatocellular carcinoma; IV=intravenous; mCRC=metastatic colorectal cancer; mMelanoma=metastatic melanoma; MSI-H=microsatellite instability-high; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42-45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Select Important Safety Information

Immune-Mediated Colitis

- OPDIVO® can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY®, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. In RCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 10% (5/49) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) of patients. In a separate Phase 3 trial of YERVOY 3 mg/kg, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that trial (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.
- 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. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Management of immune-mediated gastrointestinal adverse reactions

**Immune-mediated gastrointestinal adverse reactions**

When OPDIVO® is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Grade 1*</th>
<th>Grade 2*</th>
<th>Grade 3–4*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea:</strong> &lt;4 stools per day over baseline; colitis: asymptomatic</td>
<td><strong>Diarrhea:</strong> 4–6 stools per day over baseline; IV fluids indicated &lt;24 hours; not interfering with ADL; colitis: abdominal pain, mucus or blood in stool</td>
<td><strong>Diarrhea:</strong> ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; colitis: severe abdominal pain, medical intervention indicated, peritoneal signs;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment with OPDIVO</th>
<th>Continue treatment</th>
<th>Withhold dose†</th>
<th>Grade 3: withhold dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with OPDIVO + YERVOY</td>
<td>Continue treatment</td>
<td>Withhold dose†</td>
<td>Grade 4: permanently discontinue</td>
</tr>
</tbody>
</table>

**Symptomatic treatment**

<table>
<thead>
<tr>
<th>Steroids‡</th>
<th>For Grade 2 colitis of &gt;5 days</th>
<th>1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month§</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI tests</td>
<td>Consider lower-GI endoscopy</td>
<td></td>
</tr>
</tbody>
</table>

**Follow-up**

| Close monitoring for worsening symptoms | If improved to Grade 1 | 
| --- | --- | |
| Educate patient to report worsening immediately | • Resume treatment | |
| | • If steroids have been administered, taper steroids over at least 1 month before resuming treatment | |
| | • Permanently discontinue for recurrent colitis upon re-initiation of OPDIVO or OPDIVO + YERVOY | |

<table>
<thead>
<tr>
<th>If symptoms worsen</th>
<th>If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treat as Grade 2 or 3–4</td>
<td>In cases of corticosteroid-refractory colitis</td>
</tr>
<tr>
<td></td>
<td>• Consider repeating infectious workup to exclude alternative etiologies</td>
</tr>
<tr>
<td></td>
<td>• Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered if other causes are excluded</td>
</tr>
</tbody>
</table>

In clinical trials, some patients with immune-mediated colitis received treatments other than corticosteroids.

**OPDIVO as a single agent**

- In mMelanoma (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)
- In HCC (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)
- In aRCC and MSI-H/dMMR mCRC (OPDIVO 3 mg/kg + YERVOY 1 mg/kg)

**OPDIVO + YERVOY**

- 20% received mycophenolic acid; 20% received infliximab in addition to high-dose CS
- -23% received infliximab in addition to high-dose CS
- -23% received infliximab in addition to high-dose CS

*Grades correspond to those listed in the NCI CTCAE Version 4.0.1,2,26
†Resume treatment when adverse reaction returns to Grade 0 or 1.
‡ Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
| aRCC=advanced renal cell carcinoma; CS=corticosteroids; dMMR=mismatch repair deficient; G3=Grade 3; G4=Grade 4; GI=gastrointestinal; HCC=hepatocellular carcinoma; IV=intravenous; mCRC=metastatic colorectal cancer; mMelanoma=metastatic melanoma; MSI-H=microsatellite instability-high; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. |

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
For non-HCC patients, please see page 29 for management of immune-mediated hepatic adverse reactions.

**Select Important Safety Information**

**Immune-Mediated Hepatitis**

- **OPDIVO can cause immune-mediated hepatitis.** Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. For patients without HCC, withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3–5x the ULN, if AST/ALT is >1–3x ULN at baseline and increases to >5–10x the ULN, or if AST/ALT is >3–5x ULN at baseline and increases to >8–10x the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST/ALT increases to >10x the ULN or total bilirubin increases >3x the ULN.

<table>
<thead>
<tr>
<th>Severity*</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT is within normal limits at baseline and increases to &gt;3–5x ULN</td>
<td>Withhold dose†</td>
</tr>
<tr>
<td>AST/ALT is &gt;1–3x ULN at baseline and increases to &gt;5–10x the ULN</td>
<td></td>
</tr>
<tr>
<td>AST/ALT is &gt;3–5x ULN at baseline and increases to &gt;8–10x the ULN</td>
<td></td>
</tr>
<tr>
<td>AST/ALT increases to &gt;10x the ULN or total bilirubin increases to &gt;3x the ULN</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

*Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.1.†Resume treatment when AST/ALT returns to baseline. ALT=alanine aminotransferase; AST=aspartate aminotransferase; HCC=hepatocellular carcinoma; ULN=upper limit of normal.

**For non-HCC patients, please see page 29 for management of immune-mediated hepatic adverse reactions.**

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Management of immune-mediated hepatic adverse reactions for non-HCC patients

Immune-mediated hepatic adverse reactions

When OPDIVO® is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Grade 1*</th>
<th>Grade 2*</th>
<th>Grade 3–4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AST/ALT &gt;1–3x ULN and/or T. bili &gt;1–1.5x ULN)</td>
<td>(AST/ALT &gt;3–5x ULN or T. bili &gt;1.5–3x ULN)</td>
<td>(AST/ALT &gt;5x ULN or T. bili &gt;3x ULN)</td>
</tr>
</tbody>
</table>

**Treatment with OPDIVO or OPDIVO + YERVOY**
- Continue treatment
- Withhold dose
- Permanently discontinue

**Monitoring**
- Monitor LFTs prior to and periodically during treatment
- Increase frequency of monitoring to every 3 days
- Increase frequency of monitoring to every 1 to 2 days

**Consult**
- Gastroenterology

**Steroids**
- For moderate (Grade 2) transaminase elevations
  - 0.5 to 1 mg/kg/day prednisone equivalents
- For severe (Grade 3) or life-threatening (Grade 4) transaminase elevations with or without concomitant T. bili elevations
  - 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month

**Follow-up**

<table>
<thead>
<tr>
<th>Continue monitoring LFTs</th>
<th>If improved to Grade 1 or baseline</th>
<th>If no improvement in 3–5 days, worsens, or rebounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Resume treatment</td>
<td>• Resume routine LFT monitoring</td>
<td>• Add non-corticosteroid immunosuppressive medication</td>
</tr>
</tbody>
</table>

**If symptoms worsen**
- Treat as Grade 2 or 3–4

**If AST/ALT >5x and/or T. bili >3x ULN**
- Treat as Grade 3–4

In clinical trials, some patients with immune-mediated hepatitis received treatments other than corticosteroids.

<table>
<thead>
<tr>
<th>OPDIVO as a single agent</th>
<th>OPDIVO + YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>In mMelanoma (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)</td>
<td>In HCC (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)</td>
</tr>
<tr>
<td>In aRCC and MSI-H/dMMR mCRC (OPDIVO 3 mg/kg + YERVOY 1 mg/kg)</td>
<td></td>
</tr>
</tbody>
</table>

**Other treatments for hepatitis**
- 2 patients received mycophenolic acid in addition to high-dose CS
- ~19% received mycophenolic acid in addition to high-dose CS

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*Grades correspond to those listed in the NCI CTCAE Version 4.0. †Resume treatment when adverse reaction returns to Grade 0 or 1. ‡Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. §Add prophylactic antibiotics for opportunistic infections. Followed by corticosteroid taper over at least 1 month.

For HCC patients, please see page 28 for management of immune-mediated hepatic adverse reactions.

Select Important Safety Information

- In Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.
- In a separate Phase 3 trial of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3–5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Signs, symptoms, and grading of immune-mediated endocrinopathies

ENDOCRINOPATHIES
- Headaches that will not go away or unusual headaches
- Extreme tiredness
- Weight gain or weight loss
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Hair loss
- Feeling cold
- Constipation
- Voice gets deeper
- Excessive thirst or lots of urine
- Hypothyroidism

Select Important Safety Information

Immune-Mediated Endocrinopathies
- OPDIVO® can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

Please see additional Important Safety Information for OPDIVO and YERVOY® on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Management of immune-mediated endocrinopathies

Immune-mediated endocrinopathies

When OPDIVO® is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Treatment with OPDIVO or OPDIVO + YERVOY</th>
<th>Hypophysis</th>
<th>Adrenal insufficiency</th>
<th>Hypothyroidism/thyroiditis or hyperthyroidism</th>
<th>Type 1 diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 or 3: withhold dose*</td>
<td>Grade 2: withhold dose*</td>
<td>Grade 3: permanently discontinue</td>
<td>There are no recommended dose modifications for hypothyroidism or hyperthyroidism</td>
<td>Grade 3 hyperglycemia: withhold dose until metabolic control is achieved*</td>
</tr>
<tr>
<td>Grade 4: permanently discontinue</td>
<td>Grade 3-4: permanently discontinue</td>
<td>Grade 4 hyperglycemia: permanently discontinue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monitoring

- Evaluate endocrine function
- Consider pituitary scan
- Repeat labs in 1 to 3 weeks/MRI in 1 month if symptoms persist but normal lab/pituitary scan

Initiate medical management for control of hyperthyroidism

Consult

Consider endocrinology

Steroids

Grade 2: 1 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month

Grade 3-4: 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month

Additional therapeutic management

Administer hormone replacement therapy as clinically indicated

Administer hormone-replacement therapy for hypothyroidism

Follow-up

If improved (with or without hormone replacement)

Taper steroids over at least 1 month before resuming treatment

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Consult</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td> Grade 2</td>
<td></td>
<td>≥ Grade 2: 1 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month</td>
</tr>
<tr>
<td> Grade 3-4</td>
<td></td>
<td>Grade 3-4: 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month</td>
</tr>
</tbody>
</table>

Additional therapeutic management

Administer hormone replacement therapy as clinically indicated

Monitor thyroid function prior to and periodically during treatment

Monitor for hyperglycemia

<table>
<thead>
<tr>
<th>Type 1 diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 hyperglycemia: withhold dose until metabolic control is achieved*</td>
</tr>
</tbody>
</table>

In clinical trials, some patients with immune-mediated endocrinopathies received treatments other than corticosteroids.

### Other treatments for adrenal insufficiency

~85% received HRT

~67% received HRT

~26% received methimazole; ~9% received carbimazole; ~4% received propylthiouracil

~29% received methimazole; ~24% received carbimazole

~79% received levothyroxine

~73% received levothyroxine

~91% received levothyroxine

~81% with RCC and ~78% with CRC received levothyroxine

*Reserve treatment when adverse reaction returns to Grade 0 or 1. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Consider prophylactic antibiotics for opportunistic infections.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Signs and symptoms of immune-mediated nephritis and renal dysfunction

NEPHRITIS AND RENAL DYSFUNCTION
- Increase in serum creatinine
- Decrease in the amount of urine
- Blood in urine
- Swelling in ankles
- Loss of appetite

Select Important Safety Information

Immune-Mediated Nephritis and Renal Dysfunction

- OPDIVO® can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY® 3 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 1.7% (2/119) of patients.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42-45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Management of immune-mediated renal adverse reactions

Immune-mediated renal adverse reactions\(^{1,2,26}\)

When OPDIVO\(^\text{®}\) is administered in combination with YERVOY\(^\text{®}\), if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Grade 1*</th>
<th>Grade 2–3*</th>
<th>Grade 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Creatinine &gt;ULN and &gt;baseline but ≤1.5x baseline)</td>
<td>(Creatinine &gt;1.5x to ≤6x ULN)</td>
<td>(Creatinine &gt;6x ULN)</td>
</tr>
<tr>
<td><strong>Treatment with OPDIVO or OPDIVO + YERVOY</strong></td>
<td>Continue treatment</td>
<td>Withhold dose(^1)</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Monitor creatinine weekly</td>
<td>Monitor creatinine every 2 to 3 days</td>
</tr>
<tr>
<td><strong>Consult</strong></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Steroids(^1)</strong></td>
<td>–</td>
<td>0.5 to 1 mg/kg/day prednisone equivalents followed by a corticosteroid taper over at least 1 month</td>
</tr>
<tr>
<td><strong>Renal tests</strong></td>
<td>–</td>
<td>Consider renal biopsy</td>
</tr>
</tbody>
</table>

**Follow-up\(^{1,2}\)**

<table>
<thead>
<tr>
<th>If improved to baseline</th>
<th>If improved to Grade 1</th>
<th>If improved to Grade 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resume routine creatinine monitoring</td>
<td>Taper steroids over at least 1 month before resuming treatment with routine creatinine monitoring(^8)</td>
<td>Taper steroids over at least 1 month(^1)</td>
</tr>
<tr>
<td>If worsens</td>
<td>If worsening or no improvement</td>
<td>–</td>
</tr>
<tr>
<td>Treat as Grade 2–3 or 4</td>
<td>1 to 2 mg/kg/day prednisone equivalents</td>
<td>–</td>
</tr>
</tbody>
</table>

*Grades correspond to those listed in the NCI CTCAE Version 4.0.1,2\* Resume treatment when adverse reaction returns to Grade 0 or 1.1\*Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.1\* Consider prophylactic antibiotics for opportunistic infections.12\* Add prophylactic antibiotics for opportunistic infections.12 \(\text{IV}=\text{intravenous}; \text{NCI CTCAE}=\text{National Cancer Institute Common Terminology Criteria for Adverse Events}; \text{ULN}=\text{upper limit of normal.}"

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
**Signs and symptoms of immune-mediated skin adverse reactions**

**SKIN ADVERSE REACTIONS**
- Rash
- Itching
- Skin blistering
- Ulcers in mouth or other mucous membranes

**Select Important Safety Information**

**Immune-Mediated Skin Adverse Reactions and Dermatitis**

- **OPDIVO®** can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY® 3 mg/kg, immune-mediated rash occurred in 22.6% (92/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 35% (17/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16% (90/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 14% (17/119) of patients.

- In a separate Phase 3 trial of YERVOY 3 mg/kg, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 (2.5%) patients. 1 (0.2%) patient died as a result of toxic epidermal necrolysis. 1 additional patient required hospitalization for severe dermatitis.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including **Boxed WARNING regarding immune-mediated adverse reactions** for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Management of immune-mediated skin adverse reactions

#### Immune-mediated skin adverse reactions

When OPDIVO® is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Treatment with OPDIVO or OPDIVO + YERVOY</th>
<th>Grade 1–2* (Covering ≤30% BSA)</th>
<th>Grade 3–4* (Covering &gt;30% BSA; life-threatening consequences)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continue treatment</strong></td>
<td></td>
<td>Grade 3 rash or symptoms/signs of SJS or TEN: Withhold dose†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 4 rash or confirmed SJS or TEN: Permanently discontinue</td>
</tr>
</tbody>
</table>

Consult

Symptomatic treatment

**Administer (eg, antihistamines and topical steroids)**

For symptoms or signs of SJS or TEN

Refer the patient for specialized care for assessment and treatment

**Steroids**

Administer symptomatic treatment (eg, topical steroids)

For immune-mediated rash

1 to 2 mg/kg/day of prednisone equivalents followed by corticosteroid taper over at least 1 month

Skin test

Consult dermatology

**Consider skin biopsy**

#### Follow-up

<table>
<thead>
<tr>
<th>If symptoms persist &gt;1–2 weeks or recur</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider skin biopsy</td>
</tr>
<tr>
<td>• Withhold dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If improved to Grade 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taper steroids over at least 1 month before resuming treatment§</td>
</tr>
</tbody>
</table>

If symptoms worsen

Treat as Grade 3–4

In clinical trials, some patients with immune-mediated dermatologic adverse reactions received treatments other than systemic corticosteroids.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OPDIVO + YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPDIVO as a single agent</strong></td>
<td>In mMelanoma (OPDIVO 1 mg/kg + YERVOY 3 mg/kg)</td>
</tr>
<tr>
<td><strong>Other treatments for skin adverse reactions</strong></td>
<td>85% received topical CS</td>
</tr>
</tbody>
</table>

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*Grades correspond to those listed in the NCI CTCAE Version 4.0.129 Resume treatment when adverse reaction returns to Grade 0 or 1. †Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.15 Add prophylactic antibiotics for opportunistic infections.12

arCC=advanced renal cell carcinoma; BSA=body surface area; CS=corticosteroids; dMMR=mismatch repair deficient; HCC=hepatocellular carcinoma; IV=intravenous; mCRC=metastatic colorectal cancer; mMelanoma=metastatic melanoma; MSI-H=microsatellite instability-high; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis.

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Signs and symptoms of immune-mediated neurologic adverse reactions

- Headache
- Fever
- Tiredness
- Weakness
- Confusion
- Memory problems
- Sleepiness
- Seeing or hearing things that are not really there (hallucinations)
- Seizures
- Stiff neck

Select Important Safety Information

Immune-Mediated Encephalitis

- OPDIVO® can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. In patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one melanoma patient receiving OPDIVO 1 mg/kg with YERVOY® 3 mg/kg (0.2%) after 1.7 months of exposure. Encephalitis occurred in one RCC patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure. Encephalitis occurred in one MSI-H/dMMR mCRC patient (0.8%) receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg after 15 days of exposure.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
### Management of immune-mediated neurologic adverse reactions

#### Immune-mediated neurologic adverse reactions

- Withhold OPDIVO® in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration.
- If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper.
- Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
- When OPDIVO is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

<table>
<thead>
<tr>
<th>Grade 1* (Asymptomatic or mild symptoms)</th>
<th>Grade 2* (New-onset moderate to severe neurologic signs or symptoms)</th>
<th>Grade 3–4* (Severe symptoms; life-threatening)</th>
<th>Immune-mediated encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with OPDIVO or OPDIVO + YERVOY</td>
<td>Continue treatment</td>
<td>Withhold dose†</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Consult</td>
<td>–</td>
<td>–</td>
<td>Neurology</td>
</tr>
<tr>
<td>Steroids‡</td>
<td>–</td>
<td>Treat symptoms per local guidelines</td>
<td>1 to 2 mg/kg/day prednisone equivalents§ followed by corticosteroid taper over at least 1 month</td>
</tr>
</tbody>
</table>

#### Follow-up

<table>
<thead>
<tr>
<th>If worsens</th>
<th>If worsens or no improvement</th>
<th>If worsens or atypical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat as Grade 2 or 3–4</td>
<td>Treat as Grade 3–4</td>
<td>Consider other immunosuppressive therapies</td>
</tr>
</tbody>
</table>

*Grades correspond to those listed in the NCI CTCAE Version 4.0.†Resume treatment when adverse reaction returns to Grade 0 or 1.‡Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed.§Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.§Add prophylactic antibiotics for opportunistic infections.‡IV=intravenous; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

### Select Important Safety Information

#### Immune-Mediated Neuropathies

- In a separate Phase 3 trial of YERVOY 3 mg/kg, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Signs and symptoms of immune-mediated myocarditis\textsuperscript{13,14}

**MYOCARDITIS**

- Cardio-pulmonary and cardiac symptoms; potential signs and symptoms may include:
  - Chest pain
  - Shortness of breath
  - Fatigue
  - Palpitations
  - Syncope

- Diagnosis of myocarditis requires a high index of suspicion, and in some cases can be asymptomatic

Select Important Safety Information

Other Immune-Mediated Adverse Reactions

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO®, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY®, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
## Immune-mediated myocarditis

When OPDIVO® is administered in combination with YERVOY®, if OPDIVO is withheld, YERVOY should also be withheld.

### Treatment with OPDIVO or OPDIVO + YERVOY

<table>
<thead>
<tr>
<th>Grade 2*</th>
<th>Grade 3*</th>
<th>Grade 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms with mild to moderate activity or exertion</td>
<td>Severe with symptoms at rest or with minimal activity or exertion; intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support)</td>
</tr>
</tbody>
</table>

*Grades correspond to those listed in the NCI CTCAE Version 4.0.28 †Retreatment may be considered after recovery and completion of steroid taper.28 ‡Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.28 §Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.28

### Monitoring

- Withhold dose†
- Permanently discontinue
- Hospitalize with cardiac monitoring
- Hospitalize to intensive cardiac monitoring

### Consult/Test

- Urgent cardiology consultation for evaluation and management:
  - Troponin and BNP monitoring
  - ECG ± continuous cardiac monitoring
  - Echocardiogram
  - Cardiac MRI
- Cardiac evaluation to include:
  - Troponin and BNP monitoring
  - ECG ± continuous cardiac monitoring
  - Echocardiogram
  - Cardiac MRI
  - Myocardial biopsy if feasible

### Steroids‡§

- Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
- Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus

### Additional therapeutic management§

- Consider adding a second immunosuppressive agent
  - Additionally, for Grade 4:
  - Hospitalize/transfer to institution with expertise in intensive cardiac monitoring

### Follow-up28

**If improved**

- Taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
- Repeat cardiac MRI for post-treatment assessment and cardiology follow-up
- Retreatment may be considered after recovery and completion of steroid taper

**If worsens**

- Intensify treatment according to grade

**If no improvement**

- Consider additional immunosuppressive agent

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*BNP=B-type natriuretic peptide; ECG=electrocardiogram; IV=intravenous; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.*

Please see Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Signs, symptoms, and management of other immune-mediated adverse reactions

**Signs and symptoms may include**
- Changes in eyesight
- Severe or persistent muscle or joint pains
- Severe muscle weakness
- Chest pain
- Upper respiratory tract infection

**Management of other immune-mediated adverse reactions**
- OPDIVO® can cause other clinically significant and potentially fatal immune-mediated adverse reactions.
- If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients who received OPDIVO or OPDIVO in combination with YERVOY® and may require treatment with systemic steroids to reduce the risk of permanent vision loss.
- Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy.
- For any suspected immune-mediated adverse reactions, exclude other causes.
- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy.
- Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month.
- Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event.

Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients who received OPDIVO:

- Myocarditis
- Rhabdomyolysis
- Myositis
- Uveitis
- Iritis
- Pancreatitis
- Facial and abducens nerve paresis
- Autoimmune neuropathy
- Motor dysfunction
- Vasculitis
- Gastritis
- Duodenitis
- Polymyalgia rheumatica
- Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis)
- Aplastic anemia
- Systemic inflammatory response syndrome
- Sarcoidosis

**Select Important Safety Information**

**Other Immune-Mediated Adverse Reactions**
- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.
- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.
Signs, symptoms, and management of infusion-related reactions

Signs and symptoms may include\(^1\)
- Chills or shaking
- Itching or rash
- Flushing
- Difficulty breathing
- Dizziness
- Fever
- Feeling like passing out

Management of infusion-related reactions
- OPDIVO\(^\circ\) can cause severe infusion-related reactions, which have been reported in less than 1.0% of patients in clinical trials\(^1\)
- Infusion-related reactions were graded according to the NCI CTCAE Version 4.0\(^1,16\)
- Mild/moderate symptoms (Grade 1 or 2)\(^1,16\)
  - Interrupt or slow the rate of infusion in patients
  - Monitor patients until recovery
- Severe/life threatening (Grade 3 or 4)\(^1,16\)
  - Discontinue OPDIVO in such patients
  - To manage anaphylaxis, follow institutional protocol
  - Patient should be monitored until the treating physician is comfortable that the symptoms will not recur

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Select Important Safety Information

Infusion-Related Reactions
- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. 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\(^\circ\) 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.2% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, 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 MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY® can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests, at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Immune-Mediated Pneumonitis

- OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 10% (52/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) of patients. In NSCLC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with OPDIVO 360 mg every 4 weeks in combination with YERVOY 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with OPDIVO in combination with YERVOY only.

- In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (162/2653) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (132/2653) of patients receiving YERVOY: Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

- OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 6% (25/407) of patients including three fatal cases. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 3% (10/373) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 7% (8/119) of patients.

- In a separate Phase 3 trial of YERVOY 3 mg/kg, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that trial (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

- 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. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

Immune-Mediated Hepatitis

- OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. For patients with Grade 1 transaminase elevations for OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3 and up to 5 times the upper limit of normal (ULN), if AST/ALT is >1 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 13% (10/78) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 20% (10/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 8% (10/119) of patients.

- In Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.

- In a separate Phase 3 trial of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3-5) occurred in 8% (10/119) of patients.

Immune-Mediated Neuropathies

- In a separate Phase 3 trial of YERVOY 3 mg/kg, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.

Immune-Mediated Endocrinopathies

- OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor HCT, WBC, and platelet counts for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold OPDIVO and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

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

- In patients receiving OPDIVO® monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY® 3 mg/kg, hypophysitis occurred in 9% (36/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 4% (2/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hypophysitis occurred in 3.4% (4/119) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 5% (21/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 18% (9/49) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 1.2% (23/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hypophysitis occurred in 0.9% (17/1994) of patients.

- In a separate Phase 3 trial of YERVOY 3 mg/kg, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) patients. 1 (0.2%) patient died as a result of toxic epidermal necrolysis. 1 additional patient required hospitalization for severe dermatitis.

**Immune-Mediated Encephalitis**

- OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Based on the severity of the adverse reaction, permanently discontinue OPDIVO for immune-mediated encephalitis. In patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one melanoma patient receiving OPDIVO 1 mg/kg, resulting in 0.2% (2/1034) after 17 months of exposure. Encephalitis occurred in one RCC patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure. Encephalitis occurred in one MSI-H/dMMR mCRC patient (0.8%) receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg after 15 days of exposure.

**Other Immune-Mediated Adverse Reactions**

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducent nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

- 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 may require treatment with systemic steroids to reduce the risk of permanent vision loss.

(Continued on next page)
**Infusion-Related Reactions**

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2.

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% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, 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 MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients.

**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). 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.

**Embryo-Fetal Toxicity**

- Based on mechanism of action, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO or YERVOY and for at least 5 months after the last dose.

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

- In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone 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.

**Lactation**

- It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO or YERVOY, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

**Serious Adverse Reactions**

- In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatraemia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, 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 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=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. In Checkmate 025, 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 disseminated intravascular coagulation. 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, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 032, serious adverse reactions occurred in 45% of patients receiving OPDIVO (n=245). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, pneumonitis, pleural effusion, and dehydration. 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, diarrhea, and hypercalcemia. In Checkmate 224, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pleural effusion, pneumonitis, and pyrexia (10% and 1.0%). In Checkmate 215 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 ≥1% 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, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO.

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with YERVOY®, 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 040, 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, 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). 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. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO®-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

Common Adverse Reactions

- In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) 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 (≥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/colitis (26%), diarrhea (26%), nausea (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (≥20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 032, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=245) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diarrhea (21%), constipation (20%), and cough (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving 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%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough and dyspnea at a higher incidence than investigator’s choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent, the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), pyrexia (24%), rash (23%), constipation (20%), and upper respiratory tract infection (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=154) 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 (n=49), were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

Checkmate Trials and Patient Populations

- Checkmate 037 – previously treated metastatic melanoma; marine trial
- Checkmate 066 – previously untreated metastatic melanoma; marine trial
- Checkmate 067 – previously untreated metastatic melanoma, as a single agent or in combination with YERVOY.
- Checkmate 227 – previously untreated metastatic non-small cell lung cancer, in combination with YERVOY.
- Checkmate 9LA – previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology
- Checkmate 017 – second-line treatment of metastatic squamous non-small cell lung cancer
- Checkmate 057 – second-line treatment of metastatic non-squamous non-small cell lung cancer
- Checkmate 032 – small cell lung cancer
- Checkmate 025 – previously treated renal cell carcinoma
- Checkmate 214 – previously untreated renal cell carcinoma, in combination with YERVOY
- Checkmate 205/039 – classical Hodgkin lymphoma
- Checkmate 141 – recurrent or metastatic squamous cell carcinoma of the head and neck
- Checkmate 275 – urothelial carcinoma
- Checkmate 142 – MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY
- Checkmate 040 – hepatocellular carcinoma, as a single agent or in combination with YERVOY
- Checkmate 238 – adjuvant treatment of melanoma

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Please see Important Safety Information for OPDIVO® and YERVOY® on pages 42–45 and US Full Prescribing Information for OPDIVO and YERVOY, including **Boxed WARNING** regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.
Responses provided between 8:00 AM and 8:00 PM ET, Monday–Friday

Complications of stem cell transplant that uses donor stem cells (allogeneic) have been reported. These complications can be severe and lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

These are not all of the possible side effects of OPDIVO® (nivolumab) and OPDIVO + YERVOY® (ipilimumab). This is why your patient needs to tell you about any discomfort or changes in the way they are feeling.

Use this chart to help your patient notice and report potential side effects.

Before treatment, write down how your patient is feeling to record a baseline

After treatment begins, write down any changes that occur (especially the thyroid, pituitary, adrenal glands, and pancreas)

- Headaches that will not go away or unusual headaches
- Extreme tiredness
- Weight gain or weight loss
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Dizziness or fainting
- Hair loss
- Feeling cold
- Constipation
- Voice gets deeper
- Excessive thirst or lots of urine

(colitis that can lead to tears or holes in your intestine)

Changes in eyesight

Severe or persistent muscle or joint pains

Severe muscle weakness

Chest pain

Brain:

- Yellowing of your skin or the whites of your eyes
- Severe nausea or vomiting
- Pain on the right side of your stomach area (abdomen)
- Drowsiness
- Dark urine (tea colored)
- Bleeding or bruising more easily than normal
- Feeling less hungry than usual
- Decreased energy

Liver:

- Headache
- Fever
- Tiredness or weakness
- Confusion
- Memory problems
- Sleepiness
- Seeing or hearing things that are not really there (hallucinations)
- Seizures

Intestines:

- New or worsening cough
- Chest pain
- Shortness of breath

Hormone Glands:

Kidneys:

- Decrease in the amount of urine
- Blood in your urine
- Swelling in your ankles
- Loss of appetite

Skin:

- Skin blistering
- Ulcers in mouth or other mucous membranes

Severe Infusion Reactions:

- Chills or shaking
- Itching or rash
- Difficulty breathing
- Feeling like passing out

Other Organs:

- Stiff neck
- Rash
- Itching

Diarrhea (loose stools) or more bowel movements than usual

Blood in your stools or dark, tarry, sticky stools

Severe stomach-area (abdomen) pain or tenderness

Please see Important Safety Information for OPDIVO and YERVOY on pages 2-3, and U.S. Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY. Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the Checkmate trials.