# Immune-Mediated Adverse Reactions Management Guide

OPDIVO (nivolumab) | OPDIVO (nivolumab) + YERVOY (ipilimumab) | OPDIVO (nivolumab) + CABOMETYX (cabozantinib) tablets | Opdualag (nivolumab and relatlimab-rmbw) Injection for intravenous use | 480 mg/160 mg

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# OPDIVO® (nivolumab), OPDIVO in combination with other therapeutic agents, and Opdualag™ (nivolumab and relatlimab-rmbw) indications[1,2]

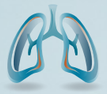
OPDIVO, as a single agent or in combination with YERVOY® (ipilimumab), is indicated for the treatment of adult patients with unresectable or metastatic melanoma.

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

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

OPDIVO, in combination with YERVOY, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

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

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

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.

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

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

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

OPDIVO (10 mg/mL), YERVOY (5 mg/mL), and Opdualag (nivolumab 12 mg/mL and relatlimab-rmbw 4 mg/mL) are injections for intravenous use.[1-3]
ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; PD-L1=programmed death-ligand 1.

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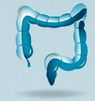


OPDIVO, as a single agent or in combination with YERVOY, is indicated for the treatment of adult and pediatric patients (12 years and older) with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with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

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

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

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

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma.

## Opdualag

Opdualag is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

Please see recommended dosing on pages 30–32.

### OPDIVO Summary of Warnings and Precautions

- OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation; 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.

### Opdualag Summary of Warnings and Precautions

- Opdualag is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, myocarditis, and other immune-mediated adverse reactions; infusion-related reactions; complications of allogenic hematopoietic stem cell transplantation (HSCT) after PD-1/PD-L1 blocking antibody; and embryo-fetal toxicity.

# Monitoring and consultation considerations for potential and suspected immune-mediated adverse reactions (IMARs)

## Considerations when managing IMARs[1,2,4-9]

**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 those of other treatments, they may need to be managed differently
- **IMARs, which may be severe or fatal, can occur in any organ system or tissue. IMARs listed herein may not include all possible IMARs**
- Prompt patient reporting of side effects may help lead to identification of IMARs
- While some patients may have to discontinue treatment, others may need to withhold treatment and may be able to resume after appropriate intervention and IMAR resolution

## Routine monitoring for potential IMARs[1-3]

- Patients treated with OPDIVO® (nivolumab) or Opdualag™ (nivolumab and relatlimab-rmbw) should be monitored at baseline and periodically during treatment
- Patients treated with OPDIVO + YERVOY® (ipilimumab) should be monitored at baseline and before each dose
- In patients treated with OPDIVO in combination with CABOMETYX® (cabozantinib), consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents
- Patients with cardiac or cardio-pulmonary symptoms treated with Opdualag should be assessed for potential myocarditis
- 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 (HSCT)
- IMARs can occur at any time during treatment and after discontinuation of therapy
- Monitor closely for symptoms and signs of underlying IMARs
- This is not an exhaustive list of clinical tests and exams

| IMAR | Recommended monitoring for OPDIVO, OPDIVO + YERVOY, Opdualag, and approved combinations with OPDIVO |
|---|---|
| **Hepatitis** | Liver enzymes |
| **Endocrinopathies** | • Adrenocorticotropic hormone levels (for OPDIVO + YERVOY only)<br>• Thyroid function<br>• Hyperglycemia |
| **Nephritis and renal dysfunction** | Serum creatinine |

## Monitoring and consultation for suspected IMARs[1-3]

- In cases of suspected IMARs, initiate appropriate workup to exclude alternative etiologies, including infection
- Institute medical management promptly, including specialty consultation as appropriate

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



# Organ systems potentially affected by IMARs[1-3]

The signs and symptoms related to potential IMARs reported with OPDIVO, OPDIVO + YERVOY, and Opdualag are listed in their specific sections. You can use the tabs or go to the indicated pages for more information.



**These are not all the possible organ systems that may be affected.[1-3]**

YERVOY may be associated with eye problems with signs and symptoms that include blurry vision, double vision or other vision problems, and eye pain or redness.[3]

Complications of allogeneic HSCT, such as graft-versus-host disease, can be fatal, and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with OPDIVO, YERVOY, and Opdualag.[1-3]

# PULMONARY: Pneumonitis
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated pneumonitis, defined as requiring the use of steroids and having no clear alternate etiology. Fatal cases have been reported. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.[1,2]

**Signs and symptoms may include[1,2]:**

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

### Management considerations for immune-mediated pneumonitis[1-3]

| Grades based on CTCAE V5.0[10] | Grade 1<br>Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Grade 2<br>Symptomatic; medical intervention indicated; limiting instrumental ADL | Grade 3–4<br>Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated<br>Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation) |
|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Withhold treatment* | Permanently discontinue treatment |
| **Management** | – | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.<br>Treatments received by some patients in clinical trials:<br>• For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (aRCC and mCRC; n=666): of the patients with pneumonitis (n=26), 8% required coadministration of another immunosuppressant with corticosteroids | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

*Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.[1,2]

ADL=activities of daily living; aRCC=advanced renal cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; mCRC=metastatic colorectal cancer; NCI=National Cancer Institute.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



# Immune-mediated pneumonitis: Summary of select clinical trial data

### Select data for all grades of immune-mediated pneumonitis[1-3]

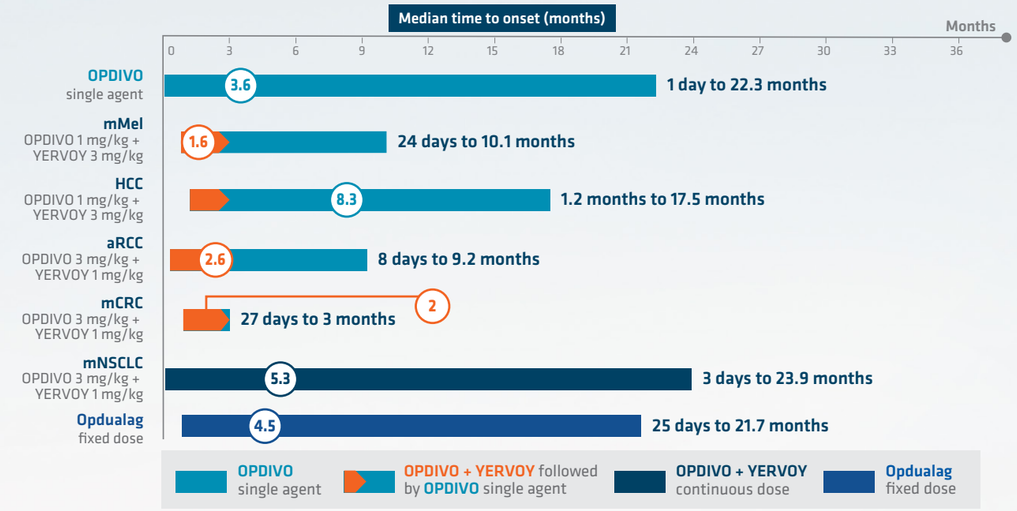
Pooled data for immune-mediated pneumonitis with OPDIVO and OPDIVO + YERVOY are provided below. In mNSCLC, 4 patients (0.7%) died due to pneumonitis. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation† |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 3.1% 61 of 1994 patients | 84% of 61 patients | 1.1% of 1994 patients | 0.8% of 1994 patients | 29% of 14 patients |
| | In cHL patients receiving OPDIVO as a single agent, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266). Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients. 31% (4/13) of patients permanently discontinued OPDIVO. 23% (3/13) of patients resumed treatment with OPDIVO after a dose delay. 25% (2/8) of patients experienced a recurrence of pneumonitis. | | | | |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 7% 31 of 456 patients | 94% of 31 patients | 2.9% of 456 patients | 3.9% of 456 patients | 31% of 13 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 3.9% 26 of 666 patients | 92% of 26 patients | 1.8% of 666 patients | 1.5% of 666 patients | 40% of 10 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** mNSCLC | 9% 50 of 576 patients | 72% of 50 patients | 5% of 576 patients | 3.6% of 576 patients | 13% of 16 patients |
| **Opdualag** mMel | 3.7% 13 of 355 patients | 85% of 13 patients | 0.8% of 355 patients | 1.4% of 355 patients | 0% of 5 patients |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

### Onset (median and range) for all grades of immune-mediated pneumonitis[11-17]




†Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1-3]

cHL=classical Hodgkin lymphoma; HCC=hepatocellular carcinoma; mMel=metastatic melanoma; mNSCLC=metastatic NSCLC; NSCLC=non-small cell lung cancer.

# GASTROINTESTINAL: Colitis
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated colitis, which may be fatal. Immune-mediated colitis is defined as requiring the use of steroids and having no clear alternate etiology.[1,2]

**Signs and symptoms may include[1,2]:**

- Diarrhea (loose stools) or more frequent bowel movements than usual
- Severe stomach area (abdominal) pain or tenderness
- Stools that are black, tarry, sticky, or have blood or mucus

### Management considerations for potential immune-mediated colitis[1,2]

| Grades based on CTCAE V5.0[10] | Grade 1<br>Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Grade 2<br>Abdominal pain; mucus or blood in stool | Grade 3<br>Severe abdominal pain; peritoneal signs | Grade 4<br>Life-threatening consequences; urgent intervention indicated |
|---|---|---|---|---|
| **Dose modification** with OPDIVO or Opdualag | Continue treatment | Withhold treatment* | For patients on **OPDIVO** or **Opdualag**, withhold treatment for Grade 3* | For patients on **OPDIVO** or **Opdualag**, permanently discontinue treatment for Grade 4 |
| **Dose modification** with OPDIVO + YERVOY | Continue treatment | Withhold treatment* | For patients on **OPDIVO + YERVOY,** permanently discontinue treatment for Grade 3 or 4 symptoms | |
| **Management** | – | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.<br>Treatments received by some patients in clinical trials:<br>• For **OPDIVO** single agent (n=1994): of the patients with colitis (n=58), 7% (n=4) received infliximab in addition to high-dose corticosteroids<br>• For **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** (mMel and HCC; n=456): of the patients with colitis (n=115), 23% received infliximab in addition to high-dose corticosteroids<br>• For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (aRCC and mCRC; n=666): of the patients with colitis (n=60), 23% received infliximab in addition to high-dose corticosteroids<br>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. | | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

*Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.[1,2]

aRCC=advanced renal cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NCI=National Cancer Institute.



# Immune-mediated colitis: Summary of select clinical trial data

### Select data for all grades of immune-mediated colitis[1-3]

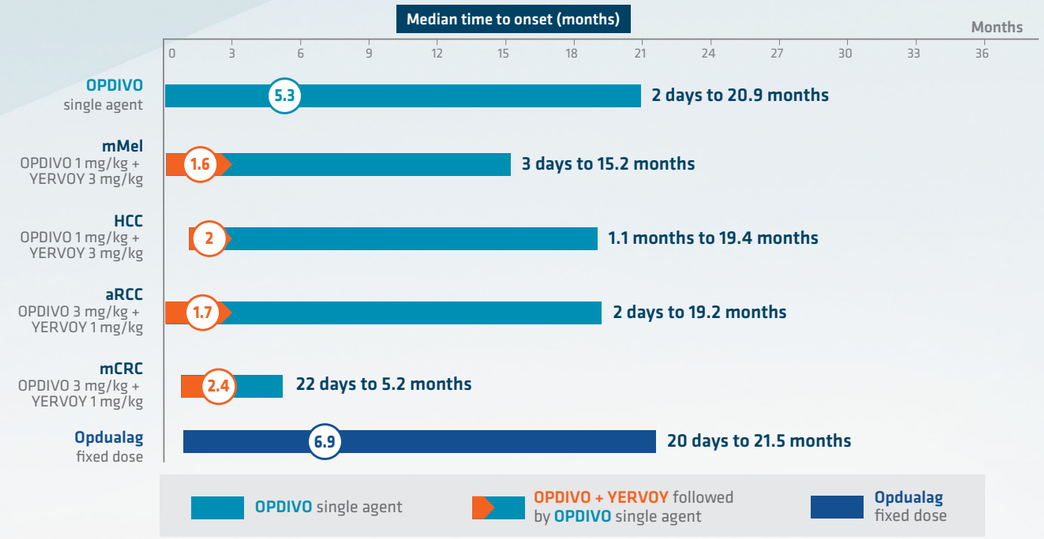
Pooled data for immune-mediated colitis with OPDIVO and OPDIVO + YERVOY are provided below. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation† |
|---|---|---|---|---|---|
| **OPDIVO** single agent | **2.9%** 58 of 1994 patients | **86%** of 58 patients | **0.7%** of 1994 patients | **0.9%** of 1994 patients | **75%** of 16 patients |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | **25%** 115 of 456 patients | **93%** of 115 patients | **14%** of 456 patients | **4.4%** of 456 patients | **56%** of 16 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | **9%** 60 of 666 patients | **95%** of 60 patients | **3.2%** of 666 patients | **2.7%** of 666 patients | **63%** of 16 patients |
| **Opdualag** mMel | **7%** 24 of 355 patients | **83%** of 24 patients | **2%** of 355 patients | **2.8%** of 355 patients | **67%** of 9 patients |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

### Onset (median and range) for all grades of immune-mediated colitis[11-14,16,17]




†Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1-3]

NSCLC=non-small cell lung cancer.

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# ENDOCRINE: Adrenal insufficiency
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), OPDIVO + CABOMETYX® (cabozantinib), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated endocrinopathies, including primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and type 1 diabetes mellitus, which can present with diabetic ketoacidosis.[1,2]

**Signs and symptoms for all immune-mediated endocrine adverse reactions may include[1,2]:**

- Headaches that will not go away or unusual headaches
- Extreme tiredness
- Weight loss or weight gain
- Dizziness or fainting
- Eye sensitivity to light
- Eye problems
- Rapid heartbeat
- Increased sweating
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Feeling more hungry or thirsty than usual
- Urinating more often than usual
- Feeling cold
- Constipation
- Voice gets deeper
- Hair loss

### Management considerations for immune-mediated adrenal insufficiency[1,2]

| Grades based on CTCAE V5.0[10] | Grade 1<br>Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Grade 2<br>Moderate symptoms; medical intervention indicated | Grade 3<br>Severe symptoms; hospitalization indicated | Grade 4<br>Life-threatening consequences; urgent intervention indicated |
|---|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Consider withholding depending on clinical severity until symptom improvement with hormone replacement.<br>Resume treatment once acute symptoms have resolved. | Withhold treatment until clinically stable or permanently discontinue depending on severity. | |
| **Management** | – | Initiate symptomatic treatment, including hormone replacement as clinically indicated.<br>Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less if clinically appropriate. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants, including corticosteroid therapy, if clinically appropriate.<br>Treatments received by some patients in clinical trials:<br>• For **OPDIVO** single agent (n=1994): of the patients with adrenal insufficiency (n=20), ~85% received HRT and 90% required systemic corticosteroids<br>• For **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** (mMel and HCC; n=456): of the patients with adrenal insufficiency (n=35), ~71% received HRT, including systemic corticosteroids<br>• For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (aRCC and mCRC; n=666): of the patients with adrenal insufficiency (n=48), ~94% received HRT, including systemic corticosteroids<br>• For **OPDIVO + CABOMETYX** (aRCC; n=320): of the patients with adrenal insufficiency (n=15), ~80% received HRT, including systemic corticosteroids<br>• For **Opdualag** (mMel; n=355): of the patients with adrenal insufficiency (n=15), 87% received HRT, and 87% required systemic corticosteroids | | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY or CABOMETYX, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

aRCC=advanced renal cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; HCC=hepatocellular carcinoma; HRT=hormone replacement therapy; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NCI=National Cancer Institute.

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# Immune-mediated adrenal insufficiency: Summary of select clinical trial data

### Select data for all grades of immune-mediated adrenal insufficiency[1,2]

Pooled data for immune-mediated adrenal insufficiency with OPDIVO and OPDIVO + YERVOY are provided below. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation* |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 1%<br>20 of 1994 patients | 35%<br>of 20 patients | 0.1%<br>of 1994 patients | 0.4%<br>of 1994 patients | 100%<br>of 4 patients† |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 8%<br>35 of 456 patients | 37%<br>of 35 patients | 0.4%<br>of 456 patients | 2%<br>of 456 patients | 100%<br>of 7 patients† |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 7%<br>48 of 666 patients | 29%<br>of 48 patients | 1.2%<br>of 666 patients | 2.1%<br>of 666 patients | 18%<br>of 11 patients |
| **OPDIVO + CABOMETYX** aRCC | 4.7%<br>15 of 320 patients | 27%<br>of 15 patients | 0.9%<br>of 320 patients | 2.8%<br>of 320 patients | 33%<br>of 6 patients |
| **Opdualag** mMel | 4.2%<br>15 of 355 patients | 33%<br>of 15 patients | 1.1%<br>of 355 patients | 0.8%<br>of 355 patients | 0%<br>of 3 patients |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing. In the aRCC trial evaluating OPDIVO in combination with CABOMETYX, OPDIVO 240 mg was administered.[1]

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]

### Onset (median and range) for all grades of immune-mediated adrenal insufficiency[11-14,16,17]


*Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1]

†All of these patients required hormone replacement therapy for their ongoing adrenal insufficiency.[1]

NSCLC=non-small cell lung cancer.

# ENDOCRINE: Hypophysitis
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. For additional signs and symptoms for all immune-mediated endocrine adverse reactions, see page 10.[1,2]

### Management considerations for immune-mediated hypophysitis[1,2]

| Grades based on CTCAE V5.0[10] | Grade 1<br>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | Grade 2<br>Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL | Grade 3<br>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL | Grade 4<br>Life-threatening consequences; urgent intervention indicated |
|---|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Consider withholding depending on clinical severity until symptom improvement with hormone replacement.<br>Resume treatment once acute symptoms have resolved. | Withhold treatment until clinically stable or permanently discontinue depending on severity. | |
| **Management** | – | Initiate hormone replacement as clinically indicated.<br>Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less if clinically appropriate. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants, including corticosteroid therapy, if clinically appropriate.<br>Treatments received by some patients in clinical trials:<br>• For **OPDIVO** single agent (n=1994): of the patients with hypophysitis (n=12), 67% received HRT, including systemic corticosteroids<br>• For **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** (mMel and HCC; n=456): of the patients with hypophysitis (n=42), 86% received HRT, and 88% required systemic corticosteroids<br>• For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (aRCC and mCRC; n=666): of the patients with hypophysitis (n=29), ~72% received HRT, including systemic corticosteroids<br>• For **Opdualag** (mMel; n=355): of the patients with hypophysitis (n=9), 100% received HRT, and 100% required systemic corticosteroids | | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

ADL=activities of daily living; aRCC=advanced renal cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; HCC=hepatocellular carcinoma; HRT=hormone replacement therapy; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NCI=National Cancer Institute.



# Immune-mediated hypophysitis: Summary of select clinical trial data

### Select data for all grades of immune-mediated hypophysitis[1,2]

Pooled data for immune-mediated hypophysitis with OPDIVO and OPDIVO + YERVOY are provided below. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation* |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 0.6%<br>12 of 1994 patients | 42%<br>of 12 patients | <0.1%<br>of 1994 patients | 0.2%<br>of 1994 patients | 0%<br>of 2 patients |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 9%<br>42 of 456 patients | 38%<br>of 42 patients | 0.9%<br>of 456 patients | 4.2%<br>of 456 patients | 11%<br>of 9 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 4.4%<br>29 of 666 patients | 59%<br>of 29 patients | 1.2%<br>of 666 patients | 2.1%<br>of 666 patients | 18%<br>of 11 patients |
| **Opdualag** mMel | 2.5%<br>9 of 355 patients | 22%<br>of 9 patients | 0.3%<br>of 355 patients | 0.6%<br>of 355 patients | – |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

### Onset (median and range) for all grades of immune-mediated hypophysitis[11-14,16,17]


*Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1]

NSCLC=non-small cell lung cancer.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# ENDOCRINE: Type 1 diabetes mellitus
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. For additional signs and symptoms of all immune-mediated endocrine adverse reactions, see page 10.[1-3]

### Management considerations for immune-mediated type 1 diabetes mellitus that can present with diabetic ketoacidosis[1-3]

| Grades based on CTCAE V5.0 for hyperglycemia[10] | Grade 1<br>Abnormal glucose above baseline with no medical intervention | Grade 2<br>Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes | Grade 3<br>Insulin therapy initiated; hospitalization indicated | Grade 4<br>Life-threatening consequences; urgent intervention indicated |
|---|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Consider withholding depending on clinical severity until symptom improvement with hormone replacement.<br>Resume treatment once acute symptoms have resolved. | Withhold treatment until clinically stable or permanently discontinue depending on severity. | |
| **Management** | Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. | | | |
| | – | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less if clinically appropriate. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants, including corticosteroid therapy, if clinically appropriate.<br>Treatments received by some patients in clinical trials:<br>• For **OPDIVO** single agent (n=1994): of the patients who developed type 1 diabetes (n=17), none required systemic corticosteroids<br>• For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (aRCC and mCRC; n=666): of the patients who developed type 1 diabetes (n=15), 7% required systemic corticosteroids | | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

aRCC=advanced renal cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; mCRC=metastatic colorectal cancer; NCI=National Cancer Institute.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



# Immune-mediated type 1 diabetes mellitus: Summary of select clinical trial data

### Select data for all grades of type 1 diabetes mellitus[1-3]

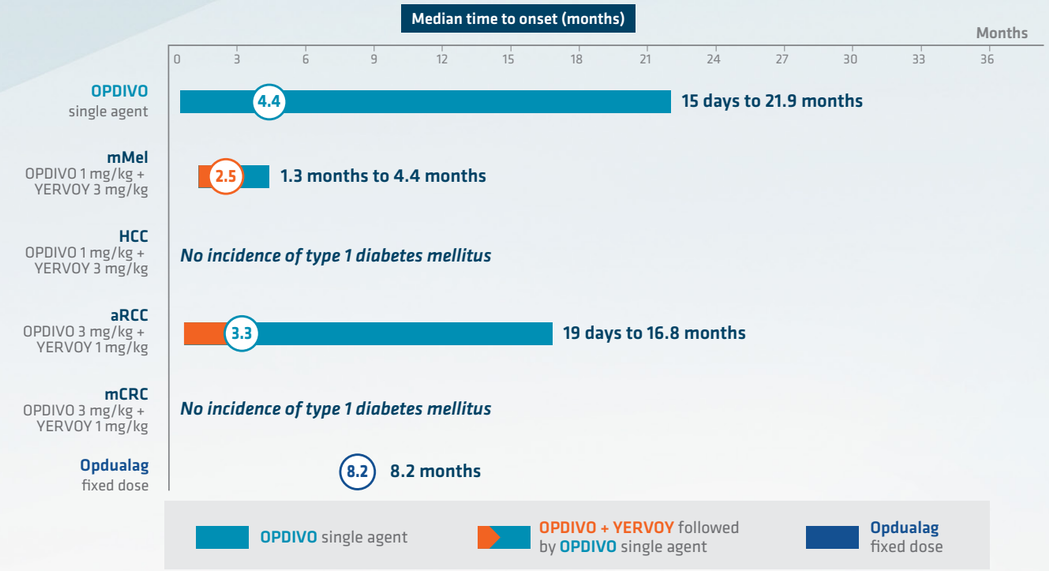
Pooled data for immune-mediated type 1 diabetes mellitus with OPDIVO and OPDIVO + YERVOY are provided below. Pooled data for OPDIVO 1 mg/kg + YERVOY 3 mg/kg are not available in the OPDIVO or YERVOY Prescribing Information for type 1 diabetes mellitus. Two cases of diabetic ketoacidosis were reported for OPDIVO single agent. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation* |
|---|---|---|---|---|---|
| **OPDIVO** single agent | **0.9%** 17 of 1994 patients | **29%** of 17 patients | **0%** of 1994 patients | **0.1%** of 1994 patients | **0%** of 2 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | **2.7%** 15 of 666 patients | **27%** of 15 patients | **0.5%** of 666 patients | **0.5%** of 666 patients | **0%** of 2 patients |
| **Opdualag** mMel | **0.3%** 1 of 355 patients | – | **0%** of 355 patients | **0%** of 355 patients | – |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

### Onset (median and range) for all grades of type 1 diabetes mellitus[11-14,16,17]




*Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1,3]

HCC=hepatocellular carcinoma; mMel=metastatic melanoma; NSCLC=non-small cell lung cancer.

# ENDOCRINE: Thyroid disorders
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated thyroid disorders, including thyroiditis, hyperthyroidism, and hypothyroidism. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. For additional signs and symptoms of all immune-mediated endocrine adverse reactions, see page 10.[1,2]

### Management considerations for immune-mediated thyroid disorders[1-3]

| Grades based on CTCAE V5.0[10] | Grade 1<br>Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Grade 2<br>Symptomatic; limiting instrumental ADL<br>Hyperthyroidism: thyroid suppression therapy indicated<br>Hypothyroidism: thyroid replacement indicated | Grade 3<br>Severe symptoms; limiting self-care ADL; hospitalization indicated | Grade 4<br>Life-threatening consequences; urgent intervention indicated |
|---|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Consider withholding depending on clinical severity until symptom improvement with hormone replacement.<br>Resume treatment once acute symptoms have resolved. | Withhold treatment until clinically stable or permanently discontinue depending on severity. | |
| **Management** | – | Initiate hormone replacement or medical management as clinically indicated.<br>Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less if clinically appropriate. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants, including corticosteroid therapy, if clinically appropriate.<br>Treatments received by some patients in clinical trials:<br>• Of patients with thyroiditis:<br>  • For **OPDIVO** single agent (n=12): 17% required systemic corticosteroids<br>  • For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (n=22): 18% required systemic corticosteroids<br>  • For **Opdualag** (n=10): 20% required systemic corticosteroids<br>• Of patients with hyperthyroidism:<br>  • For **OPDIVO** single agent (n=54): 19% received methimazole, 7% received carbimazole, 4% received propylthiouracil, and 9% required systemic corticosteroids<br>  • For **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** (n=42): 26% received methimazole, 21% received carbimazole, and 17% required systemic corticosteroids<br>  • For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (n=80): 16% received methimazole, 3% received carbimazole, and 20% required systemic corticosteroids<br>  • For **Opdualag** (n=22): 23% required systemic corticosteroids<br>• Of patients with hypothyroidism:<br>  • For **OPDIVO** single agent (n=163): 79% received levothyroxine and 3.1% required systemic corticosteroids<br>  • For **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** (n=91): 89% received levothyroxine and 2.2% required systemic corticosteroids<br>  • For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (n=122): 82% received levothyroxine and 7% required systemic corticosteroids<br>  • For **Opdualag** (n=59): none required systemic corticosteroids | | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]



# Immune-mediated thyroid disorders: Summary of select clinical trial data

### Select data for all grades of thyroid disorders (thyroiditis, hyperthyroidism, hypothyroidism)[1-3]

Pooled data for immune-mediated thyroid disorders with OPDIVO and OPDIVO + YERVOY are provided below. Pooled data for OPDIVO 1 mg/kg + YERVOY 3 mg/kg are not available in the OPDIVO or YERVOY Prescribing Information for thyroiditis. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| Thyroiditis | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation* |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 0.6%<br>12 of 1994 patients | 58%<br>of 12 patients | 0%<br>of 1994 patients | 0.2%<br>of 1994 patients | 0%<br>of 1 patient |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 2.7%<br>22 of 666 patients | 64%<br>of 22 patients | 0.2%<br>of 666 patients | 0.8%<br>of 666 patients | 0%<br>of 5 patients |
| **Opdualag** mMel | 2.8%<br>10 of 355 patients | 90%<br>of 10 patients | 0%<br>of 355 patients | 0.3%<br>of 355 patients | 0%<br>of 1 patient |
| **Hyperthyroidism** | **Incidence** | **Resolution** | **Permanently discontinued** | **Withheld treatment** | **Recurrence after re-initiation*** |
| **OPDIVO** single agent | 2.7%<br>54 of 1994 patients | 76%<br>of 54 patients | 0%<br>of 1994 patients | 0.4%<br>of 1994 patients | 0%<br>of 4 patients |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 9%<br>42 of 456 patients | 91%<br>of 42 patients | 0%<br>of 456 patients | 2.4%<br>of 456 patients | 13%<br>of 8 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 12%<br>80 of 666 patients | 85%<br>of 80 patients | 0%<br>of 666 patients | 2.3%<br>of 666 patients | 27%<br>of 11 patients |
| **Opdualag** mMel | 6%<br>22 of 355 patients | 82%<br>of 22 patients | 0%<br>of 355 patients | 0.3%<br>of 355 patients | 0%<br>of 1 patient |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

*Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1-3]

ADL=activities of daily living; aRCC=advanced renal cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NCI=National Cancer Institute; NSCLC=non-small cell lung cancer.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# Immune-mediated thyroid disorders: Summary of select clinical trial data (cont'd)

## Select data for all grades of thyroid disorders (thyroiditis, hyperthyroidism, hypothyroidism) (cont'd)[1,2]

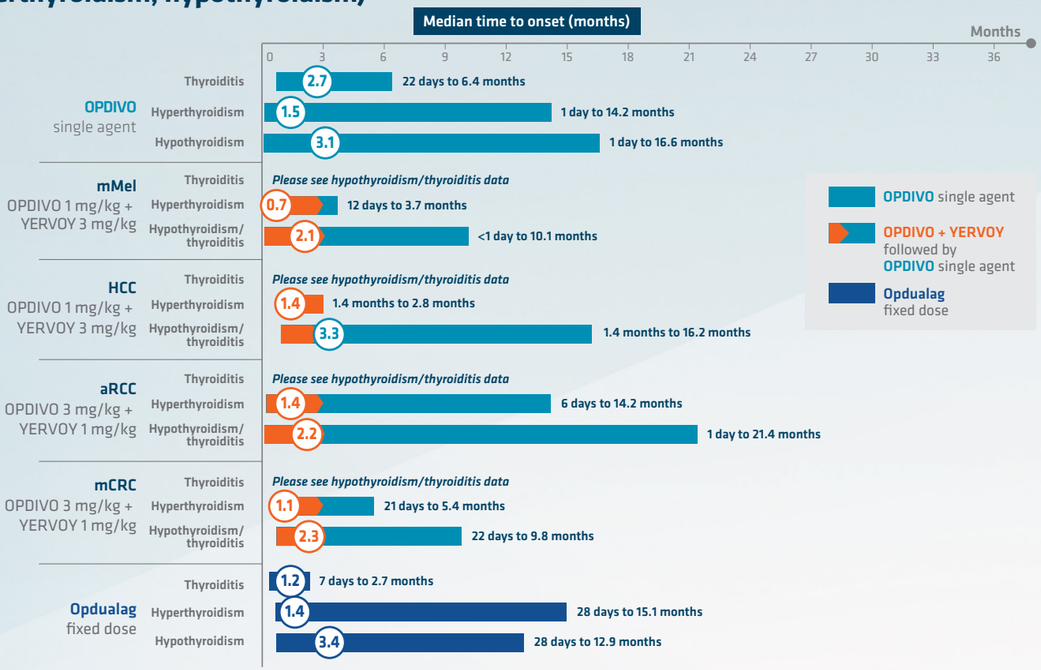
Pooled data for immune-mediated thyroid disorders with OPDIVO® (nivolumab) and OPDIVO + YERVOY® (ipilimumab) are provided below. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| Hypothyroidism | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation* |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 8% 163 of 1994 patients | 35% of 163 patients | 0% of 1994 patients | 0.5% of 1994 patients | 33% of 3 patients |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 20% 91 of 456 patients | 41% of 91 patients | 0.9% of 456 patients | 0.9% of 456 patients | 0% of 2 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 18% 122 of 666 patients | 27% of 122 patients | 0.2% of 666 patients | 1.4% of 666 patients | 20% of 5 patients |
| **Opdualag™ (nivolumab and relatlimab-rmbw)** mMel | 17% 59 of 355 patients | 12% of 59 patients | 0.3% of 355 patients | 2.5% of 355 patients | 33% of 6 patients |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

## Onset (median and range) for all grades of thyroid disorders (thyroiditis, hyperthyroidism, hypothyroidism)[11-14,16,17]




*Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1,2]

aRCC=advanced renal cell carcinoma; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NSCLC=non-small cell lung cancer.



# HEPATIC: Hepatitis and hepatotoxicity
## Management considerations

OPDIVO, OPDIVO + YERVOY, and Opdualag can cause immune-mediated hepatitis, defined as requiring the use of steroids and having no clear alternate etiology. OPDIVO + CABOMETYX® (cabozantinib) can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared with OPDIVO alone.[1,2]

**Signs and symptoms may include[1,2]:**

- Severe nausea or vomiting
- Dark urine (tea colored)
- Yellowing of the skin or the whites of the eyes
- Pain on the right side of the stomach area (abdomen)
- Bleeding or bruising more easily than normal

## Management considerations for elevated liver enzymes[1]

| | Liver enzyme elevations |
|---|---|
| **Dose modification** with **OPDIVO + CABOMETYX** | Withhold treatment if ALT or AST is >3x ULN but ≤10x ULN with concurrent total bilirubin <2x ULN until adverse reactions recover to Grades 0–1.<br>• After recovery, re-challenge with one or both of OPDIVO + CABOMETYX may be considered. If re-challenging with CABOMETYX with or without OPDIVO, refer to CABOMETYX Prescribing Information<br>Permanently discontinue treatment if ALT or AST is >10x ULN or >3x ULN with concurrent total bilirubin ≥2x ULN. |
| **Management** | Consider corticosteroid therapy for hepatic adverse reactions if OPDIVO + CABOMETYX is withheld or discontinued. |

### Select data for all grades of immune-mediated hepatotoxicity

- With the combination of **OPDIVO + CABOMETYX**, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0–1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were re-challenged with either OPDIVO (n=11) or CABOMETYX (n=9) administered as a single agent or in combination (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving OPDIVO, 2 patients receiving CABOMETYX, and 7 patients receiving both OPDIVO and CABOMETYX. For full dosing information, please see pages 30–32.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# Immune-mediated hepatitis: Management considerations (cont'd)

## Management considerations for immune-mediated hepatitis[1,2]

| | For patients with hepatitis and no tumor involvement of liver | For patients with hepatitis and tumor involvement of liver without HCC | For patients with hepatitis and tumor involvement of liver or HCC |
|---|---|---|---|
| **Dose modification** with OPDIVO® (nivolumab) | Withhold treatment* if AST/ALT increases to >3x and ≤8x ULN or total bilirubin increases to >1.5x and ≤3x ULN.<br>Permanently discontinue treatment if AST/ALT is >8x ULN or total bilirubin is >3x ULN. | Withhold treatment* if baseline AST/ALT is >1x and ≤3x ULN and increases to >5x and ≤10x ULN or baseline AST/ALT is >3x and ≤5x ULN and increases to >8x and ≤10x ULN.†<br>Permanently discontinue treatment if AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN.† | |
| **Dose modification** with OPDIVO + YERVOY® (ipilimumab) | Withhold treatment* if AST/ALT increases to >3x and ≤5x ULN or total bilirubin increases to ≥1.5x and ≤3x ULN.<br>Permanently discontinue treatment if AST/ALT is >5x ULN or total bilirubin is >3x ULN. | | Withhold treatment* if baseline AST/ALT is >1x and ≤3x ULN and increases to >5x and ≤10x ULN or baseline AST/ALT is >3x and ≤5x ULN and increases to >8x and ≤10x ULN.†<br>Permanently discontinue treatment if AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN.† |
| **Dose modification** with Opdualag™ (nivolumab and relatlimab-rmbw) | Withhold treatment* if AST/ALT increases to >3x and ≤8x ULN or total bilirubin increases to >1.5x and ≤3x ULN.<br>Permanently discontinue treatment if AST or ALT increases to more than 8 times ULN regardless of baseline or total bilirubin increases to more than 3 times ULN. | – | |
| **Management** | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less.<br>Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | | |
| **Follow-up** | Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.<br>Treatments received by some patients in clinical trials:<br>• For **OPDIVO** single agent (n=1994): of patients with hepatitis (n=35), 6% received mycophenolic acid in addition to high-dose corticosteroids<br>• For **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** (mMel and HCC; n=456): of patients with hepatitis (n=70), 9% received mycophenolic acid in addition to high-dose corticosteroids<br>• For **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** (aRCC and mCRC; n=666): of patients with hepatitis (n=48), 19% received mycophenolic acid in addition to high-dose corticosteroids | | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY or CABOMETYX® (cabozantinib), toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

*Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.[1,2]

†If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO or OPDIVO + YERVOY based on recommendations for hepatitis with no liver involvement.[1]

ALT=alanine aminotransferase; aRCC=advanced renal cell carcinoma; AST=aspartate aminotransferase; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; ULN=upper limit of normal.



# Immune-mediated hepatitis: Summary of select clinical trial data

## Select data for all grades of immune-mediated hepatitis[1,2]

Pooled data for immune-mediated hepatitis with OPDIVO and OPDIVO + YERVOY are provided below. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation‡ |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 1.8% 35 of 1994 patients | 91% of 35 patients | 0.7% of 1994 patients | 0.6% of 1994 patients | 82% of 11 patients |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 15% 70 of 456 patients | 91% of 70 patients | 8% of 456 patients | 3.5% of 456 patients | 57% of 14 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 7% 48 of 666 patients | 88% of 48 patients | 3.6% of 666 patients | 2.6% of 666 patients | 71% of 14 patients |
| **Opdualag** mMel | 6% 20 of 355 patients | 70% of 20 patients | 1.7% of 355 patients | 2.3% of 355 patients | 50% of 6 patients |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

## Onset (median and range) for all grades of immune-mediated hepatitis[11-14,16,17]


‡Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1,2]

NSCLC=non-small cell lung cancer.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# RENAL: Nephritis with renal dysfunction
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated nephritis with renal dysfunction, defined as requiring the use of steroids and having no clear alternate etiology.[1-3]

**Signs and symptoms may include[1,2]:**

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

### Management considerations for immune-mediated nephritis with renal dysfunction[1,2]

| Grades based on CTCAE V5.0 for creatinine increased[10] | Grade 1<br>Creatinine increases greater than ULN–1.5x ULN | Grade 2–3<br>Grade 2: Creatinine increases greater than 1.5–3x baseline; greater than 1.5–3x ULN<br>Grade 3: Creatinine increases to greater than 3x baseline; greater than 3–6x ULN | Grade 4<br>Creatinine increases greater than 6x ULN |
|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Withhold treatment* | Permanently discontinue treatment |
| **Management** | – | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

*Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.[1,2]

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; ULN=upper limit of normal.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



# Immune-mediated nephritis with renal dysfunction: Summary of select clinical trial data

### Select data for all grades of immune-mediated nephritis with renal dysfunction[1-3]

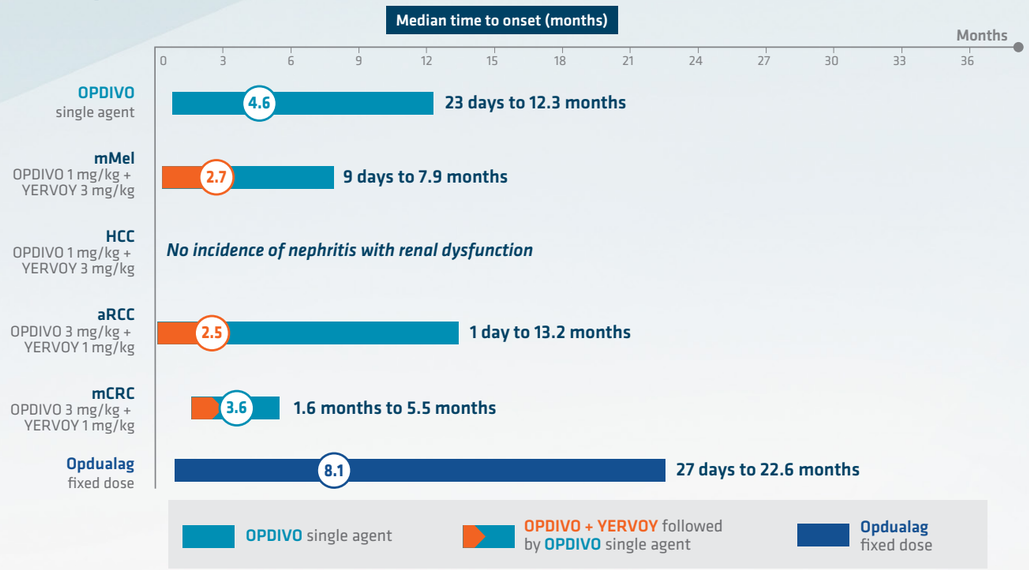
Pooled data for immune-mediated renal dysfunction with OPDIVO and OPDIVO + YERVOY are provided below. Pooled data for OPDIVO 1 mg/kg + YERVOY 3 mg/kg are not available in the OPDIVO or YERVOY Prescribing Information for renal dysfunction. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation‡ |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 1.2% 23 of 1994 patients | 78% of 23 patients | 0.3% of 1994 patients | 0.4% of 1994 patients | 14% of 7 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 4.1% 27 of 666 patients | 67% of 27 patients | 1.2% of 666 patients | 1.8% of 666 patients | 40% of 10 patients |
| **Opdualag** mMel | 2% 7 of 355 patients | 71% of 7 patients | 0.8% of 355 patients | 0.6% of 355 patients | 0% of 1 patient |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

### Onset (median and range) for all grades of immune-mediated nephritis with renal dysfunction[11-14,16,17]




‡Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1-3]

aRCC=advanced renal cell carcinoma; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NSCLC=non-small cell lung cancer.

# DERMATOLOGIC: Dermatologic adverse reactions
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and having no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), has occurred. YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS.[1-3]

**Signs and symptoms may include[1,2]:**

- Rash
- Itching
- Skin blistering or peeling
- Painful sores or ulcers in mouth, nose, throat, or genital area

### Management considerations for immune-mediated dermatologic adverse reactions[1,2]

| | **Suspected** SJS, TEN, or DRESS | **Confirmed** SJS, TEN, or DRESS |
|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Withhold treatment | Permanently discontinue treatment |
| **Management** | Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.<br>Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less if clinically appropriate. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | |
| **Follow-up** | Consider administration of other systemic immunosuppressants, including corticosteroid therapy, if clinically appropriate. | |

When OPDIVO is administered in combination with YERVOY, if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued.[1]

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



# Immune-mediated dermatologic adverse reactions: Summary of select clinical trial data

### Select data for all grades of immune-mediated rash[1,2]

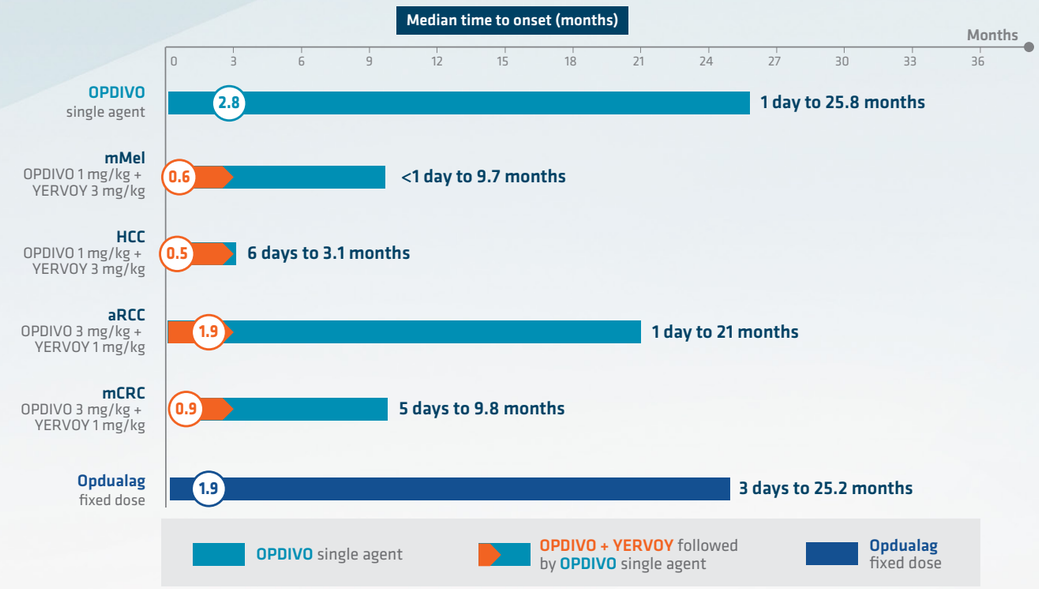
Pooled data for immune-mediated skin adverse reactions with OPDIVO and OPDIVO + YERVOY are provided below. For incidence by grade, please see the Important Safety Information on pages 34–41. For full dosing information, please see pages 30–32.

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation* |
|---|---|---|---|---|---|
| **OPDIVO** single agent | 9% 171 of 1994 patients | 72% of 171 patients | 0.3% of 1994 patients | 0.5% of 1994 patients | 33% of 9 patients |
| **OPDIVO 1 mg/kg + YERVOY 3 mg/kg** mMel and HCC | 28% 127 of 456 patients | 84% of 127 patients | 0.4% of 456 patients | 3.9% of 456 patients | 53% of 15 patients |
| **OPDIVO 3 mg/kg + YERVOY 1 mg/kg** aRCC and mCRC | 16% 108 of 666 patients | 75% of 108 patients | 0.5% of 666 patients | 2% of 666 patients | 46% of 11 patients |
| **Opdualag** mMel | 9% 33 of 355 patients | 70% of 33 patients | 0% of 355 patients | 1.4% of 355 patients | 25% of 4 patients |

In the trials that evaluated OPDIVO as a single agent and in combination with YERVOY, OPDIVO monotherapy was administered using weight-based dosing.[1]

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]

### Onset (median and range) for all grades of immune-mediated rash[11-14,16,17]




*Recurrence rates are calculated among patients who withheld therapy and then re-initiated treatment after symptom improvement.[1-2]

aRCC=advanced renal cell carcinoma; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; mMel=metastatic melanoma; NSCLC=non-small cell lung cancer.

# CARDIAC: Myocarditis
## Management considerations

OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab),* and Opdualag™ (nivolumab and relatlimab-rmbw) can cause immune-mediated myocarditis, which is defined as requiring use of steroids and having no clear alternate etiology. The diagnosis of immune-mediated myocarditis requires a high index of suspicion.[1,2,18]

**Signs and symptoms may include[2]:**

- New or worse chest pain
- Irregular heartbeat or feel like your heart is racing
- Shortness of breath
- Tiredness
- Swelling of ankles

### Management considerations for immune-mediated myocarditis[1,2]

| Grades based on CTCAE V5.0[10] | Grade 1 – | Grade 2–4<br>Grade 2: symptomatic with moderate activity or exertion<br>Grade 3: severe, with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms<br>Grade 4: life-threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support) |
|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Permanently discontinue treatment |
| **Management** | – | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less and promptly arrange cardiology consultation with diagnostic workup. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants in patients whose IMARs are not controlled with corticosteroid therapy. |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

### Select data for all grades of immune-mediated myocarditis[2]

| | Incidence | Resolution | Permanently discontinued | Withheld treatment | Recurrence after re-initiation |
|---|---|---|---|---|---|
| **Opdualag** mMel | **1.7%** 6 of 355 patients | **100%** of 6 patients | **1.7%** 6 of 355 patients | – | – |

*Immune-mediated myocarditis occurred at an incidence of <1% in patients who received OPDIVO or OPDIVO + YERVOY.[1]

CTCAE=Common Terminology Criteria for Adverse Events; IMAR=immune-mediated adverse reaction; IV=intravenous; mMel=metastatic melanoma; NCI=National Cancer Institute.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# Other immune-mediated adverse reactions

**Signs and symptoms may include[1,2]:**

- New or worse chest pain, irregular heartbeat or feel like your heart is racing, shortness of breath, tiredness, swelling of ankles
- Persistent or severe muscle pain or weakness, muscle cramps
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Low red blood cells, bruising

## Management considerations[1,2]

- When OPDIVO® (nivolumab) is administered in combination with YERVOY® (ipilimumab), if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued
- Withhold or permanently discontinue OPDIVO, OPDIVO + YERVOY, or Opdualag™ (nivolumab and relatlimab-rmbw) depending on severity
- In general, if OPDIVO, OPDIVO + YERVOY, or Opdualag requires interruption or discontinuation, administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less
- Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month
- Consider administration of other systemic immunosuppressants in patients whose IMARs are not controlled with corticosteroid therapy

## The following clinically significant IMARs occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO, OPDIVO + YERVOY, or Opdualag or were reported with the use of other PD-1/PD-L1–blocking antibodies[1,2]:

Severe or fatal cases have been reported for some of these adverse reactions.

- **Cardiac/vascular:** Myocarditis (OPDIVO and OPDIVO + YERVOY <1%, please see page 26 for more information on Opdualag myocarditis incidence rate), pericarditis, vasculitis
- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, and duodenitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, and polymyalgia rheumatica
- **Endocrine:** Hypoparathyroidism
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



## Management considerations for immune-mediated neurological toxicities[1-3]

| Grades based on CTCAE V5.0[10] | Grade 1<br>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | Grade 2<br>Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL | Grade 3–4<br>Grade 3: severe or medically significant but not life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL<br>Grade 4: life-threatening consequences; urgent intervention indicated |
|---|---|---|---|
| **Dose modification** with OPDIVO, OPDIVO + YERVOY, or Opdualag | Continue treatment | Withhold treatment* | Permanently discontinue treatment |
| **Management** | – | Administer 1 to 2 mg/kg/day prednisone or equivalent until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. | |
| **Follow-up** | – | Consider administration of other systemic immunosuppressants in patients whose IMARs are not controlled with corticosteroid therapy. | |

In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4. In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[1,2]

*Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.[1-3]

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events; IMAR=immune-mediated adverse reaction; PD-1=programmed death receptor-1; PD-L1=programmed death–ligand 1.

# Recommended dosage[1]

## OPDIVO® (nivolumab) as a single agent

| Indication | Recommended OPDIVO dosage | Duration of therapy |
|---|---|---|
| **Unresectable or metastatic melanoma** | 240 mg every 2 weeks*<br>or<br>480 mg every 4 weeks* | Until disease progression or unacceptable toxicity |
| **Metastatic non-small cell lung cancer** | | |
| **Advanced renal cell carcinoma** | | |
| **Classical Hodgkin lymphoma** | | |
| **Squamous cell carcinoma of the head and neck** | | |
| **Locally advanced or metastatic urothelial carcinoma** | | |
| **Esophageal squamous cell carcinoma** | | |
| **Adjuvant treatment of melanoma** | 240 mg every 2 weeks*<br>or<br>480 mg every 4 weeks* | Until disease recurrence or unacceptable toxicity for up to 1 year |
| **Adjuvant treatment of urothelial carcinoma (UC)** | | |
| **Adjuvant treatment of resected esophageal or gastroesophageal junction cancer** | 240 mg every 2 weeks*<br>or<br>480 mg every 4 weeks* | Until disease progression or unacceptable toxicity for a total treatment duration of 1 year |
| **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer** | Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more:<br>240 mg every 2 weeks*<br>or<br>480 mg every 4 weeks* | Until disease progression or unacceptable toxicity |
| | Pediatric patients age 12 years and older and weighing less than 40 kg:<br>3 mg/kg every 2 weeks* | |

No premedication required.
*30-minute intravenous infusion.

## OPDIVO in combination with other therapeutic agents

| Indication | Recommended OPDIVO dosage | Duration of therapy |
|---|---|---|
| **Metastatic non-small cell lung cancer expressing PD-L1 ≥1%** | 3 mg/kg every 2 weeks†<br>with YERVOY® (ipilimumab) 1 mg/kg every 6 weeks† | In combination with YERVOY until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression |
| **Metastatic or recurrent non-small cell lung cancer** | 360 mg every 3 weeks†<br>with YERVOY 1 mg/kg every 6 weeks†<br>and histology-based platinum-doublet chemotherapy every 3 weeks | In combination with YERVOY until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression |
| | | 2 cycles of histology-based platinum-doublet chemotherapy |
| **Malignant pleural mesothelioma** | 360 mg every 3 weeks†<br>with YERVOY 1 mg/kg every 6 weeks† | In combination with YERVOY until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression |

No premedication required with OPDIVO and YERVOY.
Refer to the YERVOY Prescribing Information for recommended YERVOY dosage information.
†30-minute intravenous infusion on the same day.
PD-L1=programmed death–ligand 1.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag™ (nivolumab and relatlimab-rmbw) on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



## OPDIVO in combination with other therapeutic agents (cont'd)

| Indication | Recommended OPDIVO dosage | Duration of therapy |
|---|---|---|
| **Unresectable or metastatic melanoma** | 1 mg/kg every 3 weeks†<br>with YERVOY 3 mg/kg intravenously† | In combination with YERVOY for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier |
| | 240 mg every 2 weeks†<br>or<br>480 mg every 4 weeks† | After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity |
| **Hepatocellular carcinoma** | 1 mg/kg every 3 weeks†<br>with YERVOY 3 mg/kg intravenously† | In combination with YERVOY for 4 doses |
| | 240 mg every 2 weeks†<br>or<br>480 mg every 4 weeks† | After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity |
| **Advanced renal cell carcinoma (OPDIVO in combination with YERVOY)** | 3 mg/kg every 3 weeks†<br>with YERVOY 1 mg/kg intravenously† | In combination with YERVOY for 4 doses |
| | 240 mg every 2 weeks†<br>or<br>480 mg every 4 weeks† | After completing 4 doses of combination therapy with YERVOY, administer as single agent until disease progression or unacceptable toxicity |
| **Advanced renal cell carcinoma (OPDIVO in combination with CABOMETYX® [cabozantinib])** | 240 mg every 2 weeks†<br>or<br>480 mg every 4 weeks†<br>Administer OPDIVO in combination with CABOMETYX 40 mg orally once daily without food | OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years |
| | | CABOMETYX: Until disease progression or unacceptable toxicity |
| **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer** | 3 mg/kg every 3 weeks†<br>with YERVOY 1 mg/kg intravenously† | In combination with YERVOY for 4 doses |
| | Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more:<br>240 mg every 2 weeks†<br>or<br>480 mg every 4 weeks† | After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity |
| | Pediatric patients age 12 years and older and weighing less than 40 kg:<br>3 mg/kg every 2 weeks† | |
| **Gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma** | 240 mg every 2 weeks†<br>with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks<br>or<br>360 mg every 3 weeks†<br>with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks | Until disease progression, unacceptable toxicity, or up to 2 years |

No premedication required with OPDIVO and YERVOY. No premedication required with OPDIVO and CABOMETYX.
Refer to the YERVOY Prescribing Information for recommended YERVOY dosage information.
†30-minute intravenous infusion on the same day.

# Recommended dosage[2] (cont'd)

## Opdualag™ (nivolumab and relatlimab-rmbw)

| Indication | Recommended Opdualag dosage | Duration of therapy |
|---|---|---|
| **Unresectable or metastatic melanoma** | For adult patients and pediatric patients 12 years of age or older weighing at least 40 kg*:<br>480 mg nivolumab and 160 mg relatlimab every 4 weeks (30-minute intravenous infusion) | Until disease progression or unacceptable toxicity |

No premedication required with Opdualag.
*The recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg, and pediatric patients younger than 12 years of age has not been established.



# Infusion-related reactions

**Signs and symptoms may include[1,2]:**

- Itching or rash
- Shortness of breath or wheezing
- Dizziness
- Fever
- Chills or shaking
- Flushing
- Feel like passing out
- Back or neck pain

## Management considerations for infusion-related reactions[1-3,10]

- When OPDIVO® (nivolumab) is administered in combination with YERVOY® (ipilimumab), if OPDIVO is withheld or discontinued, YERVOY should also be withheld or discontinued
- OPDIVO, OPDIVO + YERVOY, or Opdualag can cause severe infusion-related reactions
- Mild or moderate symptoms (Grade 1 or 2)*: Interrupt or slow the rate of infusion
- Severe or life-threatening symptoms (Grade 3 or 4)*: Permanently discontinue treatment

*In trials that evaluated OPDIVO as a single agent or in combination with YERVOY, toxicity was graded per NCI CTCAE V4.[1]
In a trial that evaluated Opdualag, toxicity was graded per NCI CTCAE V5.0.[2]

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

## OPDIVO SELECT IMPORTANT SAFETY INFORMATION

**Infusion-Related Reactions**

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 4.2% (5/119) of patients. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

## Opdualag SELECT IMPORTANT SAFETY INFORMATION

**Infusion-Related Reactions**

- Opdualag can cause severe infusion-related reactions. Discontinue Opdualag in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild to moderate infusion-related reactions. In patients who received Opdualag as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# OPDIVO® (nivolumab) Important Safety Information

See Opdualag™ (nivolumab and relatlimab-rmbw) Important Safety Information on pages 39-41.

**Severe and Fatal Immune-Mediated Adverse Reactions**

- Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY® (ipilimumab). Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

- OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 7% (31/456) of patients, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3.9% (26/666) of patients, including Grade 3 (1.4%) and Grade 2 (2.6%). In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%). Four patients (0.7%) died due to pneumonitis.
- 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, including Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

- OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated colitis occurred in 25% (115/456) of patients, including Grade 4 (0.4%), Grade 3 (14%) and Grade 2 (8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated colitis occurred in 9% (60/666) of patients, including Grade 3 (4.4%) and Grade 2 (3.7%).

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%).
- OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. In patients receiving OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients.

Immune-Mediated Endocrinopathies

- OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.
- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). In patients receiving OPDIVO and cabozantinib, adrenal insufficiency occurred in 4.7% (15/320) of patients, including Grade 3 (2.2%) and Grade 2 (1.9%).
- In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).
- In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).
- In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).
- In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).
- In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, diabetes occurred in 2.7% (15/666) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

Immune-Mediated Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.
- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).
- In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular:* myocarditis, pericarditis, vasculitis; *nervous system:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue:* myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.
- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system:* autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular:* angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal:* pancreatitis (1.3%); *other (hematologic/immune):* conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.
- Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

**Infusion-Related Reactions**

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with

*(continued on next page)*

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# OPDIVO® (nivolumab) Important Safety Information (cont'd)

See Opdualag™ (nivolumab and relatlimab-rmbw) Important Safety Information on pages 39-41.

### Infusion-Related Reactions (cont'd)

severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY® (ipilimumab) 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 4.2% (5/119) of patients. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

### 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 OPDIVO or YERVOY. 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 OPDIVO or YERVOY and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and 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 randomized 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

- There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 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, hyponatremia, 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 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). 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. 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 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. 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 057, fatal adverse reactions occurred; these included events of infection (7 patients, including one case of *Pneumocystis jirovecii* pneumonia), pulmonary embolism (4 patients), and limbic encephalitis (1 patient). In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis. In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥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 274, serious adverse reactions occurred in 30% of patients receiving OPDIVO (n=351). The most frequent serious adverse reaction reported in ≥2% of patients receiving OPDIVO was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. 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 Attraction-3, serious adverse reactions occurred in 38% of patients receiving OPDIVO (n=209). Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease, and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%). In Checkmate 577, serious adverse reactions occurred in 33% of patients receiving OPDIVO (n=532). A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal reaction of myocardial infarction occurred in one patient who received OPDIVO. In Checkmate 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation.

### Common Adverse Reactions

- In Checkmate 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 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%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). 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 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY were fatigue (43%), musculoskeletal pain (38%), rash (34%), diarrhea (32%), dyspnea (27%), nausea (24%), decreased appetite (24%), cough (23%), and pruritus (21%).

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Please see additional Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# OPDIVO® (nivolumab) Important Safety Information (cont'd)

**Common Adverse Reactions (cont'd)**

In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%). In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%) and upper respiratory tract infection (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). 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 (14%) and dyspnea (14%) 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 274, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=351) were rash (36%), fatigue (36%), diarrhea (30%), pruritus (30%), musculoskeletal pain (28%), and urinary tract infection (22%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent (n=74), the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), cough (26%), 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® (ipilimumab) (n=119), 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 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 Attraction-3, the most common adverse reactions (≥20%) in OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%). In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=532) were fatigue (34%), diarrhea (29%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%). In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%).

**Clinical Trials and Patient Populations**

**Checkmate 037**–previously treated metastatic melanoma

**Checkmate 066**–previously untreated metastatic melanoma

**Checkmate 067**–previously untreated metastatic melanoma, as a single agent or in combination with YERVOY

**Checkmate 238**–adjuvant treatment of melanoma

**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 743**–previously untreated unresectable malignant pleural mesothelioma, in combination with YERVOY

**Checkmate 214**–previously untreated renal cell carcinoma, in combination with YERVOY

**Checkmate 9ER**–previously untreated renal cell carcinoma, in combination with cabozantinib

**Checkmate 025**–previously treated renal cell carcinoma

**Checkmate 205/039**–classical Hodgkin lymphoma

**Checkmate 141**–recurrent or metastatic squamous cell carcinoma of the head and neck

**Checkmate 275**–previously treated advanced or metastatic urothelial carcinoma

**Checkmate 274**–adjuvant treatment of urothelial carcinoma

**Checkmate 142**–MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY

**Checkmate 040**–hepatocellular carcinoma, in combination with YERVOY

**Attraction-3**–esophageal squamous cell carcinoma

**Checkmate 577**–adjuvant treatment of esophageal or gastroesophageal junction cancer

**Checkmate 649**–previously untreated advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma



# Opdualag™ (nivolumab and relatlimab-rmbw) Important Safety Information

**Severe and Fatal Immune-Mediated Adverse Reactions**

- Immune-mediated adverse reactions (IMARs) listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
- IMARs which may be severe or fatal, can occur in any organ system or tissue. IMARs can occur at any time after starting treatment with a LAG-3 and PD-1/PD-L1 blocking antibodies. While IMARs usually manifest during treatment, they can also occur after discontinuation of Opdualag. Early identification and management of IMARs are essential to ensure safe use. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying IMARs. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected IMARs, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if Opdualag requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose IMARs are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

- Opdualag can cause immune-mediated pneumonitis, which may be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.7% (13/355) of patients receiving Opdualag, including Grade 3 (0.6%), and Grade 2 (2.3%) adverse reactions. Pneumonitis led to permanent discontinuation of Opdualag in 0.8% and withholding of Opdualag in 1.4% of patients.

Immune-Mediated Colitis

- Opdualag can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.
- Immune-mediated diarrhea or colitis occurred in 7% (24/355) of patients receiving Opdualag, including Grade 3 (1.1%) and Grade 2 (4.5%) adverse reactions. Colitis led to permanent discontinuation of Opdualag in 2% and withholding of Opdualag in 2.8% of patients.

Immune-Mediated Hepatitis

- Opdualag can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.
- Immune-mediated hepatitis occurred in 6% (20/355) of patients receiving Opdualag, including Grade 4 (0.6%), Grade 3 (3.4%), and Grade 2 (1.4%) adverse reactions. Hepatitis led to permanent discontinuation of Opdualag in 1.7% and withholding of Opdualag in 2.3% of patients.

Immune-Mediated Endocrinopathies

- Opdualag can cause primary or secondary adrenal insufficiency, hypophysitis, thyroid disorders, and Type 1 diabetes mellitus, which can be present with diabetic ketoacidosis. Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).
- For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. In patients receiving Opdualag, adrenal insufficiency occurred in 4.2% (15/355) of patients receiving Opdualag, including Grade 3 (1.4%) and Grade 2 (2.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of Opdualag in 1.1% and withholding of Opdualag in 0.8% of patients.
- Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Hypophysitis occurred in 2.5% (9/355) of patients receiving Opdualag, including Grade 3 (0.3%) and Grade 2 (1.4%) adverse reactions. Hypophysitis led to permanent discontinuation of Opdualag in 0.3% and withholding of Opdualag in 0.6% of patients.
- Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Thyroiditis occurred in 2.8% (10/355) of patients receiving Opdualag, including Grade 2 (1.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of Opdualag. Thyroiditis led to withholding of Opdualag in 0.3% of patients. Hyperthyroidism occurred in 6% (22/355) of patients receiving Opdualag, including Grade 2 (1.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of Opdualag. Hyperthyroidism led to withholding of Opdualag in 0.3% of patients. Hypothyroidism occurred in 17% (59/355) of patients receiving Opdualag, including Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of Opdualag in 0.3% and withholding of Opdualag in 2.5% of patients.
- Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated. Diabetes occurred in 0.3% (1/355) of patients receiving Opdualag, a Grade 3 (0.3%) adverse reaction, and no cases of diabetic ketoacidosis. Diabetes did not lead to the permanent discontinuation or withholding of Opdualag in any patient.

*(continued on next page)*

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

# Opdualag™ (nivolumab and relatlimab-rmbw) Important Safety Information (cont'd)

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

Immune-Mediated Nephritis with Renal Dysfunction

- Opdualag can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear etiology. In patients receiving Opdualag, immune-mediated nephritis and renal dysfunction occurred in 2% (7/355) of patients, including Grade 3 (1.1%) and Grade 2 (0.8%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of Opdualag in 0.8% and withholding of Opdualag in 0.6% of patients.
- Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Immune-Mediated Dermatologic Adverse Reactions

- Opdualag can cause immune-mediated rash or dermatitis, defined as requiring use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug Rash with eosinophilia and systemic symptoms has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.
- Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).
- Immune-mediated rash occurred in 9% (33/355) of patients, including Grade 3 (0.6%) and Grade 2 (3.4%) adverse reactions. Immune-mediated rash did not lead to permanent discontinuation of Opdualag. Immune-mediated rash led to withholding of Opdualag in 1.4% of patients.

Immune-Mediated Myocarditis

- Opdualag can cause immune-mediated myocarditis, which is defined as requiring use of steroids and no clear alternate etiology. The diagnosis of immune-mediated myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, withhold dose, promptly initiate high dose steroids (prednisone or methylprednisolone 1 to 2 mg/kg/day) and promptly arrange cardiology consultation with diagnostic workup. If clinically confirmed, permanently discontinue Opdualag for Grade 2-4 myocarditis.
- Myocarditis occurred in 1.7% (6/355) of patients receiving Opdualag, including Grade 3 (0.6%), and Grade 2 (1.1%) adverse reactions. Myocarditis led to permanent discontinuation of Opdualag in 1.7% of patients.

Other Immune-Mediated Adverse Reactions

- The following clinically significant IMARs occurred at an incidence of <1% (unless otherwise noted) in patients who received Opdualag or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *Cardiac/Vascular*: pericarditis, vasculitis; *Nervous System*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *Ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other IMARs, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal*: pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis; *Musculoskeletal and Connective Tissue*: myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatica; *Endocrine*: hypoparathyroidism; *Other (Hematologic/Immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

**Infusion-Related Reactions**

- Opdualag can cause severe infusion-related reactions. Discontinue Opdualag in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild to moderate infusion-related reactions. In patients who received Opdualag as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

**Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

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

**Embryo-Fetal Toxicity**

- Based on its mechanism of action and data from animal studies, Opdualag 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 Opdualag for at least 5 months after the last dose of Opdualag.

**Lactation**

- There are no data on the presence of Opdualag in human milk, the effects on the breastfed child, or the effect on milk production. Because nivolumab and relatlimab may be excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Opdualag and for at least 5 months after the last dose.

**Serious Adverse Reactions**

- In Relativity-047, fatal adverse reaction occurred in 3 (0.8%) patients who were treated with Opdualag; these included hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis. Serious adverse reactions occurred in 36% of patients treated with Opdualag. The most frequent serious adverse reactions reported in ≥1% of patients treated with Opdualag were adrenal insufficiency (1.4%), anemia (1.4%), colitis (1.4%), pneumonia (1.4%), acute myocardial infarction (1.1%), back pain (1.1%), diarrhea (1.1%), myocarditis (1.1%), and pneumonitis (1.1%).

**Common Adverse Reactions**

- The most common adverse reactions reported in ≥20% of the patients treated with Opdualag were musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%).
- The most common laboratory abnormalities that occurred in ≥20% of patients treated with Opdualag were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).
- Please see U.S. Full Prescribing Information for Opdualag.

Please see Important Safety Information for OPDIVO® (nivolumab) and YERVOY® (ipilimumab) on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**



**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2022. **2.** Opdualag [package insert]. Princeton, NJ: Bristol-Myers Squibb Company, 2022. **3.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2021. **4.** National Cancer Institute. Immunotherapy side effects. Published September 24, 2019. Accessed April 23, 2021. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/side-effects. **5.** Yu DP, Cheng X, Liu ZD, Xu SF. Comparative beneficiary effects of immunotherapy against chemotherapy in patients with advanced NSCLC: meta-analysis and systematic review. *Oncol Lett*. 2017;14(2):1568-1580. **6.** Kornblau S, Benson AB, Catalano R, Schadendorf D. Management of cancer treatment–related diarrhea: issues and therapeutic strategies. *J Pain Symptom Manage*. 2000;19(2):118-129. **7.** Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res*. 2015;4(5):560-575. **8.** Weber JS, Postow M, Lao CD, et al. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist*. 2016;21(10):1230-1240. **9.** Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8(49). **10.** National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Published November 27, 2017. Accessed April 23, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. **11.** Data on file. NIVO 582. Princeton, NJ: Bristol-Myers Squibb Company; 2015. **12.** Data on file. NIVO 194. Princeton, NJ: Bristol-Myers Squibb Company; 2015. **13.** Data on file. NIVO 361. Princeton, NJ: Bristol-Myers Squibb Company; 2017. **14.** Data on file. NIVO 376. Princeton, NJ: Bristol-Myers Squibb Company; 2017. **15.** Data on file. NIVO 563. Princeton, NJ: Bristol-Myers Squibb Company; 2015. **16.** Data on file. NIVO 518. Princeton, NJ: Bristol-Myers Squibb Company; 2019. **17.** Data on file. RELA 0003. Princeton, NJ: Bristol-Myers Squibb Company; 2021. **18.** Public Disclosure. 00053330. Princeton, NJ: Bristol-Myers Squibb Company; 2019.

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**Responses provided between 8:00 AM and 8:00 PM ET, Monday–Friday**

***For healthcare professionals***

The following resources are available to download at **www.OPDIVOpatientmanagement.com**

**Patient Monitoring Checklist**

A tool to help nurses identify the signs and symptoms of immune-mediated adverse reactions (IMARs) in patients receiving OPDIVO® (nivolumab), OPDIVO + YERVOY® (ipilimumab), or Opdualag™ (nivolumab and relatlimab-rmbw). Contacting the patient and reviewing this checklist once weekly is recommended.

**The 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.

***For patients and caregivers***

The following resources are available to download at **www.OPDIVO.com**

**Resources for personalized assistance**

A patient support program designed to help patients and their caregivers better understand their therapy, including live support with a care counselor for patients who have been prescribed OPDIVO, OPDIVO + YERVOY, or Opdualag. Available at **www.OPDIVOwithyou.com** and **www.OpdualagWithYou.com**

**Patient Pocket Guide**

Patient resource containing OPDIVO, OPDIVO + YERVOY, and Opdualag IMAR symptoms and healthcare provider contact information.

Please see Important Safety Information for OPDIVO and YERVOY on pages 34–38 and for Opdualag on pages 39–41, and U.S. Full Prescribing Information for OPDIVO, YERVOY, and Opdualag. **Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.**

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