Nivolumab (OPDIVO®), nivolumab-based combinations, and nivolumab and relatlimab-rmbw (Opdualag™)* indications by tumor type[1,2]

Click on any icon below to see the indications.

Non-small cell lung cancer (NSCLC)
Metastatic/recurrent or early stage disease

Renal cell carcinoma (RCC)
Advanced disease

Gastroesophageal cancers
Adjuvant therapy and metastatic disease

Urothelial carcinoma (UC)
Adjuvant therapy and locally advanced or metastatic disease

Melanoma
Adjuvant therapy and advanced disease

Other tumor types

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*Relatlimab-rmbw (Opdualag) is currently only indicated for unresectable or metastatic melanoma.
NCCN=National Comprehensive Cancer Network.

SUMMARY OF WARNINGS AND PRECAUTIONS

- Opdualag, OPDIVO, and YERVOY® are 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, and other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); and embryo-fetal toxicity. In addition, Opdualag is associated with immune-mediated myocarditis and OPDIVO is associated with increased mortality in patients with multiple myeloma when added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag on pages 37–38, and US 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®-based indications in non-small cell lung cancer (NSCLC)[1]

Click on any of the icons below to learn more about the NCCN recommendation for that indication.

Earlier stages

Neoadjuvant treatment of resectable NSCLC

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

Metastatic disease

PD-L1 ≥1% mNSCLC

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

mNSCLC

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.

r/m NSCLC

OPDIVO, in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; mNSCLC=metastatic NSCLC; NCCN=National Comprehensive Cancer Network; PD-L1=programmed death ligand 1; r/m=recurrent or metastatic.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO 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.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag™ (nivolumab and relatlimab-rmbw) on pages 37–38, and US 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®-based indications in renal cell carcinoma (RCC)[1]

Click on any of the icons below to learn more about the NCCN recommendation for that indication.

Advanced disease

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

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

aRCC
OPDIVO as a single agent is indicated for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy.

aRCC=advanced RCC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO 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 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.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag™ (nivolumab and relatlimab-rmbw) on pages 37–38, and US 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®-based indications in gastroesophageal cancer[1]

Click on any of the icons below to learn more about the NCCN recommendation for that indication.

Earlier stages

Adjuvant treatment of EC or GEJC

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

Advanced/metastatic disease

Advanced or metastatic ESCC

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

Advanced or metastatic ESCC

OPDIVO, in combination with YERVOY®, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC.

aESCC

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

Advanced or metastatic GC, GEJC, and EAC

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

aESCC=advanced ESCC; EAC=esophageal adenocarcinoma; EC=esophageal cancer; GC=gastric cancer; GEJC=gastroesophageal junction cancer; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO 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.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag™ (nivolumab and relatlimab-rmbw) on pages 37–38, and US 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®-based and Opdualag™* indications in melanoma[1,2]

Click on any of the icons below to learn more about the NCCN recommendation for that indication.

Earlier stages

Adjuvant treatment of melanoma

OPDIVO is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Unresectable/metastatic disease

mMelanoma

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

mMelanoma

OPDIVO, in combination with YERVOY®, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

mMelanoma

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

*Opdualag is currently only indicated for unresectable or metastatic melanoma.

NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO 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.

Opdualag 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 additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag on pages 37–38, and US 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® indications in urothelial carcinoma (UC)[1]

Click on any of the icons below to learn more about the NCCN recommendation for that indication.

Earlier stages

Adjuvant treatment of UC

OPDIVO is indicated for the adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.

Locally advanced/metastatic disease

mUC

OPDIVO is indicated for the treatment of adult patients with locally advanced or metastatic UC 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.

mUC=metastatic UC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Infusion-Related Reactions

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

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36, for Opdualag™ (nivolumab and relatlimab-rmbw) on pages 37–38, and US 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®-based indications in other tumor types[1]

Click on any of the icons below to learn more about the NCCN recommendation for that indication.

Advanced/metastatic disease

uMPM

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

aHCC

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.

r/m SCCHN

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 platinum-based therapy.

MSI-H/dMMR metastatic CRC

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.

r/p cHL

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 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.

aHCC=advanced HCC; NCCN=National Comprehensive Cancer Network; r/m=recurrent or metastatic; r/p=relapsed or progressed; uMPM=unresectable MPM.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO 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 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 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.

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag™ (nivolumab and relatlimab-rmbw) on pages 37–38, and US 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.

Nivolumab (OPDIVO®) + chemotherapy: an NCCN recommendation for non-small cell lung cancer (NSCLC)[3]

NCCN Category 2A

Neoadjuvant nivolumab (OPDIVO) and platinum-doublet chemotherapy* is recommended as a Category 2A treatment option for eligible patients with resectable (tumors ≥4 cm or node positive†) NSCLC, regardless of PD-L1 expression.

- **Checkmate 816**
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- All patients with resectable NSCLC should be evaluated for preoperative therapy, with strong consideration for nivolumab (OPDIVO) + chemotherapy* for those patients with tumors ≥4 cm or node positive† and no contraindications to immune checkpoint inhibitors‡

Please see updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*Platinum-doublet chemo q3w for 3 cycles: any histology: carboplatin and paclitaxel or cisplatin and paclitaxel; NSQ: cisplatin and pemetrexed; SQ: cisplatin and gemcitabine. Chemotherapy regimens for patients not candidates for cisplatin-based therapy: NSQ: carboplatin and pemetrexed; SQ: carboplatin and gemcitabine. †Per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria. ‡Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or exon 21 L858R, *ALK* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors. Otherwise, refer to the Neoadjuvant Systemic Therapy for Patients Not Candidates for Immune Checkpoint Inhibitors.

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NCCN=National Comprehensive Cancer Network; NSQ=non-squamous; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; q3w=every 3 weeks; SQ=squamous.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- In Checkmate 816, serious adverse reactions occurred in 30% of patients (n=176) who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy.

OPDIVO Common Adverse Reactions

- In Checkmate 816, the most common (>20%) adverse reactions in the OPDIVO plus chemotherapy arm (n=176) were nausea (38%), constipation (34%), fatigue (26%), decreased appetite (20%), and rash (20%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

1L mNSCLC

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): an NCCN recommendation for non-small cell lung cancer (NSCLC)[3]

NCCN Category 1,
Other recommended

Nivolumab (OPDIVO) and ipilimumab (YERVOY) is recommended as a Category 1, other recommended, first-line therapy option for eligible patients with advanced or metastatic NSCLC with PD-L1 1%–49%, or as a useful in certain circumstances, Category 1, first-line therapy option for eligible patients with metastatic NSCLC with PD-L1 ≥50%, and performance status 0–2, who are *EGFR, ALK, ROS1, BRAF* V600E, *NTRK1/2/3, MET*ex14, and *RET* negative, and with no contraindications to immunotherapy.

- **Checkmate 227**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines® for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

1L=first line; ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; mNSCLC=metastatic NSCLC; NCCN=National Comprehensive Cancer Network; NSQ=non-squamous; NTRK=neurotrophic tyrosine receptor kinase; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; ROS1=ROS proto oncogene 1, receptor tyrosine kinase; SQ=squamous.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

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

OPDIVO Common Adverse Reactions

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

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

1L r/mNSCLC

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®) + chemotherapy: an NCCN recommendation for non-small cell lung cancer (NSCLC)[3]

NCCN Category 1,
Other recommended

Nivolumab (OPDIVO) and ipilimumab (YERVOY) with platinum-doublet chemotherapy* is recommended as a Category 1, other recommended, first-line therapy option for eligible patients with recurrent or metastatic NSCLC regardless of PD-L1 expression and performance status 0–1 (PD-L1 <1%) or 0–2 (PD-L1 ≥1%), who are *EGFR, ALK, ROS1, BRAF* V600E, *NTRK1/2/3, MET*ex14, *KRAS* G12C, *HER2,* and *RET* negative, and with no contraindications to PD-1 or PD-L1 inhibitors.

- **Checkmate 9LA**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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*Histology-based chemotherapy; NSQ: pemetrexed + carboplatin or cisplatin; SQ: paclitaxel + carboplatin.

1L=first line; ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; HER2=human epidermal growth factor receptor 2; NCCN=National Comprehensive Cancer Network; NTRK=neurotrophic tyrosine receptor kinase; NSQ=non-squamous; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; r/m=recurrent or metastatic; ROS1=ROS proto oncogene 1, receptor tyrosine kinase; SQ=squamous.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

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

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

2L mNSCLC

Nivolumab (OPDIVO®): an NCCN recommendation for metastatic non-small cell lung cancer (NSCLC)[3]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) is recommended as a Category 1, preferred subsequent-line therapy option for patients with metastatic NSCLC with progression on or after platinum-based chemotherapy.

- **Checkmate 017**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

2L=second line; mNSCLC=metastatic NSCLC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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).

OPDIVO Common Adverse Reactions

- 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.

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): an NCCN recommendation for advanced clear cell renal cell carcinoma (RCC)[4]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) and ipilimumab (YERVOY) is recommended as a Category 1, preferred first-line therapy option for patients with intermediate- or poor-risk advanced clear cell RCC.

- **Checkmate 214**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

1L=first line; aRCC=advanced RCC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

OPDIVO Common Adverse Reactions

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

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

1L aRCC

Nivolumab (OPDIVO®) + cabozantinib (CABOMETYX®): an NCCN recommendation for advanced clear cell renal cell carcinoma (RCC)[4]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) and cabozantinib (CABOMETYX) is recommended as a Category 1, preferred first-line therapy option for patients with favorable-, intermediate-, or poor-risk advanced clear cell RCC.

- **Checkmate 9ER**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

1L=first line; aRCC=advanced RCC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

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

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®): an NCCN recommendation for advanced clear-cell renal cell carcinoma (RCC)[4]

NCCN Category 2A

Nivolumab (OPDIVO) is recommended as a Category 2A, second-line therapy option for patients with advanced clear-cell RCC who have received prior anti-angiogenic therapy.

- **Checkmate 025**
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

2L=second line; aRCC=advanced RCC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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.

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Adjuvant EC/GEJC

Nivolumab (OPDIVO®): an NCCN recommendation for esophageal or gastroesophageal junction cancer (EC or GEJC)[5]

NCCN Category 1

Nivolumab (OPDIVO) is recommended as a Category 1, adjuvant therapy option for completely resected EC or GEJC with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy.

- **Checkmate 577**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

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

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

1L GC, GEJC, EAC

Nivolumab (OPDIVO®): an NCCN recommendation for gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC, GEJC, and EAC)[5,6]

NCCN Category 1, Preferred
PD-L1 CPS ≥5

NCCN Category 2B
PD-L1 CPS <5

Nivolumab (OPDIVO), in combination with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, is recommended as a Category 1 and Category 2B* first-line therapy option for adult patients with unresectable, advanced, recurrent, or metastatic *HER2* overexpression negative GC, GEJC, or EAC.

- **Checkmate 649**[6]
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*Category 2B recommendation is for GEJC and EAC only.[6]

1L=first line; CPS=combined positive score; HER2=human epidermal growth factor receptor 2; NCCN=National Comprehensive Cancer Network; PD-L1=programmed death ligand 1.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- In Checkmate 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation.

OPDIVO Common Adverse Reactions

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

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

1L ESCC

Nivolumab (OPDIVO®): an NCCN recommendation for metastatic esophageal squamous cell carcinoma (ESCC)[5]

NCCN Category 2A, Preferred

Nivolumab (OPDIVO), in combination with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin or cisplatin, is recommended as a Category 2A, preferred first-line therapy option for adult patients with unresectable, advanced, recurrent, or metastatic ESCC.

- **Checkmate 648**
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

1L=first line; HER2=human epidermal growth factor receptor 2; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- In Checkmate 648, serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy (n=310). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury.

OPDIVO Common Adverse Reactions

- In Checkmate 648, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=310) were nausea (65%), decreased appetite (51%), fatigue (47%), constipation (44%), stomatitis (44%), diarrhea (29%), and vomiting (23%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

1L ESCC

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): an NCCN recommendation for esophageal squamous cell carcinoma (ESCC)[5]

NCCN Category 2A, Preferred

Nivolumab (OPDIVO) and ipilimumab (YERVOY) is recommended as a Category 2A preferred first-line therapy option for adult patients with unresectable, advanced, recurrent, or metastatic ESCC.

- **Checkmate 648**
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

1L=first line; HER2=human epidermal growth factor receptor 2; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- In Checkmate 648, serious adverse reactions occurred in 69% of patients receiving OPDIVO in combination with YERVOY (n=322). The most frequent serious adverse reactions reported in ≥2% who received OPDIVO in combination with YERVOY were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with YERVOY; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

OPDIVO Common Adverse Reactions

- In Checkmate 648, the most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with YERVOY were rash (31%), fatigue (28%), pyrexia (23%), nausea (22%), diarrhea (22%), and constipation (20%).

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

2L aESCC

Nivolumab (OPDIVO®): an NCCN recommendation for esophageal squamous cell carcinoma (ESCC)[5]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) is recommended as a Category 1 preferred second-line treatment option for adult patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

- **Attraction-3**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

2L=second line; aESCC=advanced ESCC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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%).

OPDIVO Common Adverse Reactions

- In Attraction-3, the most common adverse reactions (≥20%) in OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®): NCCN recommendations for urothelial carcinoma (UC)[7]

NCCN Category 2A,
Other recommended

NCCN Category 2B,
Other recommended

Nivolumab (OPDIVO) may be considered as a Category 2A adjuvant treatment option for patients with UC* who:

- Have not received neoadjuvant cisplatin† and have pT3, pT4a, or pN+ bladder cancer‡
- Have received neoadjuvant cisplatin† and are ypT2–ypT4a§ or ypN+‡

Nivolumab (OPDIVO) may be considered as a Category 2B adjuvant treatment option for patients with upper tract GU tumors (renal pelvis and ureter) who:

- Have not received platinum-based neoadjuvant chemotherapy and are pT3–4 or pN+‡

- **Checkmate 274**[1,7]
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
- Adjuvant cisplatin-based chemotherapy should be discussed (preferred) with patients who have not received cisplatin neoadjuvant treatment

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*Recommendations are for stage II and IIIA muscle invasive bladder cancer and upper tract GU tumors previously treated with platinum neoadjuvant chemotherapy.[7] †Platinum-based chemotherapy for upper tract GU tumors.[7] ‡Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure is not improved, and for whom the risk of side effects is acceptable.[7] §T4 for upper tract GU tumors.[7]

GU=genitourinary; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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%).

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®): an NCCN recommendation for metastatic urothelial carcinoma (UC)[7]

NCCN Category 2A,
Alternative Preferred

Nivolumab (OPDIVO) is recommended as a Category 2A, second-line therapy option for patients with locally advanced or metastatic UC who:

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

- **Checkmate 275**[1]
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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2L=second line; mUC=metastatic UC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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.

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®): an NCCN recommendation for the adjuvant treatment of melanoma[8]

NCCN Category 1

Nivolumab (OPDIVO) is recommended as a Category 1 option for adjuvant systemic therapy for stage III and stage IV melanoma in patients with no evidence of disease after complete resection.*

- **Checkmate 238**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*Category 1 recommendation for the following: patients with AJCC 7th Edition stage IIIB/C sentinel node–positive disease, stage III and clinically positive nodes (following wide excision and therapeutic lymph node dissection [TLND]), resectable nodal recurrence (following complete resection and TLND if not previously done), and resected stage IV disease (no evidence of disease).

AJCC=American Joint Committee on Cancer; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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 816, serious adverse reactions occurred in 30% of patients (n=176) who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy.

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

Nivolumab and relatlimab-rmbw (Opdualag™): NCCN recommendations for metastatic or unresectable cutaneous melanoma[8]

NCCN Category 1, Preferred	Nivolumab and relatlimab-rmbw (Opdualag) is recommended as a Category 1, preferred first-line treatment option for metastatic or unresectable cutaneous melanoma.
NCCN Category 2A, Preferred	Nivolumab and relatlimab-rmbw (Opdualag) is recommended as a Category 2A, preferred second-line or subsequent treatment option for metastatic or unresectable cutaneous melanoma.

- **RELATIVITY-047**[2]
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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1L=first line; 2L=second line; mMelanoma=metastatic melanoma; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

Opdualag Serious Adverse Reactions

- In Relativity-047, fatal adverse reactions 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%).

Opdualag Common Adverse Reactions and Laboratory Abnormalities

- 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 additional Important Safety Information for Opdualag on pages 37-38 and US Full Prescribing Information for Opdualag.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): an NCCN recommendation for unresectable or metastatic melanoma[8]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) and ipilimumab (YERVOY) is recommended as a Category 1, preferred first-line systemic therapy option for metastatic or unresectable disease regardless of *BRAF* mutation status.

- **Checkmate 067**[1]
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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1L=first line; MEK=mitogen-activated protein kinase; mMelanoma=metastatic melanoma; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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%).

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

Nivolumab (OPDIVO®): an NCCN recommendation for unresectable or metastatic melanoma[8]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) is recommended as a Category 1, first-line treatment option for patients with unresectable or metastatic melanoma.

- **Checkmate 066**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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1L=first line; mMelanoma=metastatic melanoma; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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%).

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

1L Mesothelioma

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): an NCCN recommendation for unresectable pleural mesothelioma (PM)[9]

NCCN Category 1, Preferred

Nivolumab (OPDIVO) and ipilimumab (YERVOY) is recommended as a Category 1, preferred first-line systemic therapy option for eligible patients with unresectable PM.*

- **Checkmate 743**
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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*Nivolumab/ipilimumab is a preferred regimen for patients with biphasic, sarcomatoid, or epithelioid histologies.

1L=first line; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

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

OPDIVO Common Adverse Reactions

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

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

2L SCCHN

Nivolumab (OPDIVO®): an NCCN recommendation for recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)[10]

NCCN Category 1

Nivolumab (OPDIVO) is recommended as a Category 1, subsequent therapy option for patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy.

- **Checkmate 141**[1]
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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2L=second line; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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.

OPDIVO Common Adverse Reactions

- 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.

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

Subsequent-line aHCC

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): an NCCN recommendation for hepatocellular carcinoma (HCC)[11]

NCCN Category 2A,
Other recommended

Nivolumab (OPDIVO) and ipilimumab (YERVOY) is recommended as a Category 2A, subsequent-line systemic therapy option for certain patients with advanced HCC with disease progression.*†‡

- **Checkmate 040**
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*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.
†Child-Pugh class A only. ‡For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
2L=second line; aHCC=advanced HCC; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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.

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.
Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the clinical trials.

2L+ MSI-H/dMMR mCRC

Nivolumab (OPDIVO®) or nivolumab + ipilimumab (YERVOY®): an NCCN recommendation for metastatic colorectal cancer (CRC)[12]

NCCN Category 2A	Nivolumab (OPDIVO) is recommended as a Category 2A second-line therapy option for microsatellite instability-high or mismatch repair deficient metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*
NCCN Category 2B	Nivolumab (OPDIVO) with ipilimumab (YERVOY) is recommended as a Category 2B second-line therapy option for microsatellite instability-high or mismatch repair deficient metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*

- **Checkmate 142**
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*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.[1]

2L=second line; dMMR=mismatch repair deficient; mCRC=metastatic CRC; MSI-H=microsatellite instability-high; NCCN=National Comprehensive Cancer Network.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

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

OPDIVO Common Adverse Reactions

- In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent (n=74), the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), 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 (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%).

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

Nivolumab (OPDIVO®): an NCCN recommendation for classical Hodgkin lymphoma (cHL)[13]

NCCN Category 2A

Nivolumab (OPDIVO) is recommended as a Category 2A therapy option for adult patients with relapsed/refractory cHL:

- For disease refractory to at least 3 prior lines of therapy (ages 18-60 years)

- **Checkmate 205/039**[1]
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Please see updated NCCN Guidelines for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

NCCN=National Comprehensive Cancer Network; r/p=relapsed or progressed.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO Serious Adverse Reactions

- 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.

OPDIVO Common Adverse Reactions

- 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%).

Please see additional Important Safety Information for OPDIVO and YERVOY® (ipilimumab) on pages 31–36 and US Full Prescribing Information for OPDIVO and YERVOY.

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

OPDIVO® Important Safety Information

Severe and Fatal Immune-Mediated Adverse Reactions

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

Immune-Mediated Pneumonitis

- OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune- mediated pneumonitis occurred in 3.1% (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.

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OPDIVO® Important Safety Information (cont'd)

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

Immune-Mediated Endocrinopathies (cont'd)

- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 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, other transplant (including corneal graft) rejection.

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OPDIVO® Important Safety Information (cont'd)

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

- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: 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 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 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 816, serious adverse reactions occurred in 30% of patients (n=176) who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse

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OPDIVO® Important Safety Information (cont'd)

Serious Adverse Reactions (cont'd)

reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy. 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 648, serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy (n=310). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury. In Checkmate 648, serious adverse reactions occurred in 69% of patients receiving OPDIVO in combination with YERVOY (n=322). The most frequent serious adverse reactions reported in ≥2% who received OPDIVO in combination with YERVOY were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with YERVOY; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome. 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,

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OPDIVO® Important Safety Information (cont'd)

Serious Adverse Reactions (cont'd)

and disseminated intravascular coagulation. In Checkmate 76K, serious reactions occurred in 18% of patients receiving OPDIVO (n=524). Adverse reactions which resulted in permanent discontinuation of OPDIVO in >1% of patients included arthralgia (1.7%), rash (1.7%), and diarrhea (1.1%). A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). The most frequent Grade 3-4 lab abnormalities reported in ≥1% of OPDIVO-treated patients were increased lipase (2.9%), increased AST (2.2%), increased ALT (2.1%), lymphopenia (1.1%), and decreased potassium (1.0%).

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 816, the most common (>20%) adverse reactions in the OPDIVO plus chemotherapy arm (n=176) were nausea (38%), constipation (34%), fatigue (26%), decreased appetite (20%), and rash (20%). 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%). 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 (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 648, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=310) were nausea (65%), decreased appetite (51%), fatigue (47%), constipation (44%), stomatitis (44%), diarrhea (29%), and vomiting (23%). In Checkmate 648, the most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with YERVOY were rash (31%), fatigue (28%), pyrexia (23%), nausea (22%), diarrhea (22%), and constipation (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%). In Checkmate 76K, the most common adverse reactions (≥20%) reported with OPDIVO (n=524) were fatigue (36%), musculoskeletal pain (30%), rash (28%), diarrhea (23%) and pruritus (20%).

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OPDIVO® Important Safety Information (cont'd)

Clinical Trials and Patient Populations

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 649–previously untreated advanced or metastatic gastric cancer, gastroesophageal junction and esophageal adenocarcinoma

Checkmate 577–adjuvant treatment of esophageal or gastroesophageal junction cancer

Checkmate 238–adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma

Checkmate 76K–adjuvant treatment of patients 12 years of age and older with completely resected Stage IIB or Stage IIC melanoma

Checkmate 274–adjuvant treatment of urothelial carcinoma

Checkmate 275–previously treated advanced or metastatic urothelial carcinoma

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

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

Attraction-3–esophageal squamous cell carcinoma

Checkmate 648–previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma

Checkmate 040–hepatocellular carcinoma, in combination with YERVOY

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

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 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 816–neoadjuvant non-small cell lung cancer, in combination with platinum-doublet chemotherapy

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

Checkmate 025–previously treated renal cell carcinoma

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

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

Checkmate 205/039–classical Hodgkin lymphoma

Please see additional Important Safety Information for OPDIVO and YERVOY on pages 31–36, for Opdualag™ (relatlimab-rmbw) on pages 37–38, and US 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™ 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.

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).

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Opdualag™ Important Safety Information (cont'd)

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

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, other transplant (including corneal graft) 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 and 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 reactions 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 and Laboratory Abnormalities

- 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%).

Clinical Trial and Patient Populations

RELATIVITY-047–previously untreated unresectable or metastatic melanoma

Please see additional Important Safety Information for OPDIVO® (nivolumab) and YERVOY® (ipilimumab) on pages 31–36, for Opdualag on pages 37–38, and US 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® (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** OPDUALAG™ (nivolumab and relatlimab-rmbw) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.5.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed April 13, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.1.2024. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed June 21, 2023. 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