



## **Bristol Myers Squibb and Exelixis Announce Positive Topline Results from Pivotal Phase 3 CheckMate -9ER Trial Evaluating Opdivo® (nivolumab) in Combination with CABOMETYX® (cabozantinib) in Previously Untreated Advanced Renal Cell Carcinoma**

April 20, 2020

***Study met primary endpoint of significantly improving progression-free survival, and secondary endpoints of overall survival and objective response rate vs. sunitinib***

***Opdivo in combination with CABOMETYX demonstrates clinically meaningful efficacy results across all endpoints and preliminary assessment showing a favorable safety profile***

PRINCETON, N.J. & ALAMEDA, Calif.--(BUSINESS WIRE)--Apr. 20, 2020-- [Bristol Myers Squibb](#) (NYSE: BMY) and [Exelixis, Inc.](#) (NASDAQ: EXEL) today announced that CheckMate -9ER, a pivotal Phase 3 trial evaluating *Opdivo*® (nivolumab) in combination with *CABOMETYX*® (cabozantinib) compared to sunitinib in previously untreated advanced or metastatic renal cell carcinoma (RCC), met its primary endpoint of progression-free survival (PFS) at final analysis, as well as the secondary endpoints of overall survival (OS) at a pre-specified interim analysis, and objective response rate (ORR).

The safety profiles of *Opdivo* and *CABOMETYX* observed in the trial reflect the known safety profiles of the immunotherapy and tyrosine kinase inhibitor components in first-line RCC.

"The results from the pivotal CheckMate -9ER trial clearly demonstrate the combination of cabozantinib plus nivolumab provides a clinically meaningful benefit in the key efficacy measures of progression-free survival and overall survival for previously untreated kidney cancer patients," said Dr. Toni Choueiri, Director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute and Jerome and Nancy Kohlberg Professor of Medicine at Harvard Medical School. "Preliminary assessment of the data shows the combination of a 40mg dose of cabozantinib plus nivolumab demonstrated a favorable safety profile. If approved, this combination may become an important new first-line option for patients with metastatic renal cell carcinoma. We look forward to presenting detailed results at an upcoming congress."

"The positive topline results from the Phase 3 CheckMate -9ER trial evaluating *Opdivo* in combination with *CABOMETYX* build on our understanding of *Opdivo*-based regimens, and we look forward to working with global health authorities to help bring this new combination regimen to previously untreated patients, a population that despite recent advances, remains in need of additional therapeutic options that extend survival," said Brian Lamon, Ph.D., development lead, genitourinary cancers, Bristol Myers Squibb. "We would like to thank the patients who participated in this trial, as well as the investigators and site personnel for their perseverance during the conduct of this study and in delivering this important result for patients in the midst of the COVID-19 pandemic."

"Given the growing body of data showing that *CABOMETYX* may create a more immune-permissive tumor environment that may enhance response to immune checkpoint inhibitors, we have been eagerly awaiting the results for the combination of cabozantinib and nivolumab in previously untreated renal cell carcinoma," said Gisela Schwab, M.D., president, product development and medical affairs and chief medical officer, Exelixis. "We're delighted that the trial met its primary endpoint of progression-free survival as well as the secondary endpoints of overall survival and objective response rate, demonstrating consistent benefit for the combination in previously untreated renal cell carcinoma patients. We look forward to our continued collaboration with Bristol Myers Squibb as we work toward regulatory filings in the near future."

The companies plan to submit detailed results of CheckMate -9ER for presentation at an upcoming medical conference. More information about this trial is available at [ClinicalTrials.gov](#).

### **About CheckMate -9ER**

CheckMate -9ER is an open-label, randomized, multi-national Phase 3 trial evaluating patients with previously untreated advanced or metastatic renal cell carcinoma. Patients are randomized 1:1 to *Opdivo* and *CABOMETYX* or sunitinib. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS) and objective response rate (ORR). The primary efficacy analysis is comparing the doublet combination versus sunitinib in all randomized patients. The trial is sponsored by Bristol Myers Squibb and Ono Pharmaceutical Co and co-funded by Exelixis, Ipsen and Takeda Pharmaceutical Company Limited.

### **About Renal Cell Carcinoma**

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults, accounting for more than 140,000 deaths worldwide each year. RCC is approximately twice as common in men as in women, with the highest rates of the disease in North America and Europe. Globally, the five-year survival rate for those diagnosed with metastatic, or advanced, kidney cancer is 12.1%.

### **Bristol Myers Squibb: Advancing Cancer Research**

At Bristol Myers Squibb, patients are at the center of everything we do. The goal of our cancer research is to increase quality, long-term survival and make cure a possibility. We harness our deep scientific experience, cutting-edge technologies and discovery platforms to discover, develop and deliver novel treatments for patients.

Building upon our transformative work and legacy in hematology and Immuno-Oncology that has changed survival expectations for many cancers, our researchers are advancing a deep and diverse pipeline across multiple modalities. In the field of immune cell therapy, this includes registrational CAR T cell agents for numerous diseases, and a growing early-stage pipeline that expands cell and gene therapy targets, and technologies. We are

developing cancer treatments directed at key biological pathways using our protein homeostasis platform, a research capability that has been the basis of our approved therapies for multiple myeloma and several promising compounds in early- to mid-stage development. Our scientists are targeting different immune system pathways to address interactions between tumors, the microenvironment and the immune system to further expand upon the progress we have made and help more patients respond to treatment. Combining these approaches is key to delivering new options for the treatment of cancer and addressing the growing issue of resistance to immunotherapy. We source innovation internally, and in collaboration with academia, government, advocacy groups and biotechnology companies, to help make the promise of transformational medicines a reality for patients.

### **About Opdivo®**

*Opdivo* is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response. By harnessing the body's own immune system to fight cancer, *Opdivo* has become an important treatment option across multiple cancers.

*Opdivo*'s leading global development program is based on Bristol Myers Squibb's scientific expertise in the field of Immuno-Oncology, and includes a broad range of clinical trials across all phases, including Phase 3, in a variety of tumor types. To date, the *Opdivo* clinical development program has treated more than 35,000 patients. The *Opdivo* trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from *Opdivo* across the continuum of PD-L1 expression.

In July 2014, *Opdivo* was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. *Opdivo* is currently approved in more than 65 countries, including the United States, the European Union, Japan and China. In October 2015, the Company's *Opdivo* and *Yervoy* combination regimen was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 50 countries, including the United States and the European Union.

### **About CABOMETYX®**

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with HCC who have been previously treated with sorafenib. CABOMETYX tablets have also received regulatory approvals in the European Union, Japan and additional countries and regions worldwide. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the United States and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited for the commercialization and further clinical development of cabozantinib for all future indications in Japan. Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the United States.

### **U.S. FDA-APPROVED INDICATIONS FOR OPDIVO®**

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma.

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

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

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

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

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

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

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adults and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate

and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

OPDIVO® (nivolumab) is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

## **IMPORTANT SAFETY INFORMATION**

### **WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

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

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

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

#### **Immune-Mediated Pneumonitis**

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) of patients.

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

#### **Immune-Mediated Colitis**

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 7% (8/119) of patients.

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

Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

#### **Immune-Mediated Hepatitis**

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. For patients without HCC, withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to  $>3$  and up to 5 times the upper limit of normal (ULN), if AST/ALT is  $>1$  and up to 3 times ULN at baseline and increases to  $>5$  and up to 10 times the ULN, and if AST/ALT is  $>3$  and up to 5 times ULN at baseline and increases to  $>8$  and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to  $>10$  times the ULN or total bilirubin increases  $>3$  times the ULN. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 13% (51/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 8% (10/119) of patients.

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

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations  $>5x$  the ULN or total bilirubin elevations  $>3x$  the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%.

#### **Immune-Mediated Neuropathies**

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

### **Immune-Mediated Endocrinopathies**

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

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 9% (36/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hypophysitis occurred in 3.4% (4/119) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 5% (21/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (41/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 5.9% (7/119) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving this dose of OPDIVO with YERVOY. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients. Hyperthyroidism occurred in 12% (66/547) of patients receiving this dose of OPDIVO with YERVOY. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 15% (18/119) of patients. Hyperthyroidism occurred in 12% (14/119) of patients. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, diabetes occurred in 1.5% (6/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies.

### **Immune-Mediated Nephritis and Renal Dysfunction**

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

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

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

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

### **Immune-Mediated Encephalitis**

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

### **Other Immune-Mediated Adverse Reactions**

Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis,

myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

### **Infusion Reactions**

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate study 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 patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients.

### **Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

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

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

### **Embryo-Fetal Toxicity**

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

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

In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### **Lactation**

It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from an OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue breastfeeding during treatment with YERVOY and for 3 months following the final 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 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 032, serious adverse reactions occurred in 45% of patients receiving OPDIVO (n=245). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, pneumonitis, pleural effusions, and dehydration. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY and in 43% of patients receiving sunitinib. 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 patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. 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 142 in

MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in  $\geq 2\%$  of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in  $\geq 2\%$  of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in  $\geq 2\%$  of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

### Common Adverse Reactions

In Checkmate 037, the most common adverse reaction ( $\geq 20\%$ ) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 017 and 057, the most common adverse reactions ( $\geq 20\%$ ) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 032, the most common adverse reactions ( $\geq 20\%$ ) in patients receiving OPDIVO (n=245) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diarrhea (21%), constipation (20%), and cough (20%). In Checkmate 025, the most common adverse reactions ( $\geq 20\%$ ) 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 214, the most common adverse reactions ( $\geq 20\%$ ) reported in patients treated with OPDIVO plus YERVOY (n=547) vs sunitinib (n=535) were fatigue (58% vs 69%), rash (39% vs 25%), diarrhea (38% vs 58%), musculoskeletal pain (37% vs 40%), pruritus (33% vs 11%), nausea (30% vs 43%), cough (28% vs 25%), pyrexia (25% vs 17%), arthralgia (23% vs 16%), decreased appetite (21% vs 29%), dyspnea (20% vs 21%), and vomiting (20% vs 28%). In Checkmate 205 and 039, the most common adverse reactions ( $\geq 20\%$ ) 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 ( $\geq 10\%$ ) in patients receiving OPDIVO (n=236) were cough and dyspnea at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions ( $\geq 20\%$ ) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent, the most common adverse reactions ( $\geq 20\%$ ) 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, the most common adverse reactions ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) in patients receiving OPDIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). In Checkmate 238, the most common adverse reactions ( $\geq 20\%$ ) 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 a separate Phase 3 study of YERVOY 3 mg/kg, the most common adverse reactions ( $\geq 5\%$ ) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

### Recommended Dose Modifications

Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue in patients with severe or life-threatening infusion reactions.

Endocrine: Withhold YERVOY for symptomatic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving  $< 7.5$  mg prednisone or equivalent per day. Permanently discontinue YERVOY for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving  $< 7.5$  mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

### Immune-Mediated Enterocolitis

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms. Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for  $> 1$  week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent). Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to  $\leq$  Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3-5 days or recurring after symptom improvement, if other causes are excluded. In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal (diarrhea of  $\geq 7$  stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%) and

moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis. Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids. In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 enterocolitis occurred in 68 patients (14%). Seven (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications.

Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

### **Immune-Mediated Hepatitis**

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY. Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution. Withhold YERVOY in patients with Grade 2 hepatotoxicity. Permanently discontinue YERVOY in patients with Grade 3-4 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids. In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5× the ULN or total bilirubin elevations >3× the ULN; Grade 3-5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4%. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5× but ≤5× the ULN or total bilirubin elevation >1.5× but ≤3× the ULN; Grade 2). In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-4 immune-mediated hepatitis occurred in 51 patients (11%) and moderate Grade 2 immune-mediated hepatitis occurred in 22 patients (5%). Liver biopsy performed in 6 patients with Grade 3-4 hepatitis showed evidence of toxic or autoimmune hepatitis.

### **Immune-Mediated Dermatitis**

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically; administer topical or systemic corticosteroids if there is no improvement within 1 week. Withhold YERVOY in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 YERVOY-treated patients (2.5%); 1 patient (0.2%) died as a result of toxic epidermal necrolysis and 1 additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis. In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-4 immune-mediated dermatitis occurred in 19 patients (4%). There were 99 patients (21%) with moderate Grade 2 dermatitis.

### **Immune-Mediated Neuropathies**

Immune-mediated neuropathies, including fatal cases, can occur with YERVOY. Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities). Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities), such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management for severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. In patients receiving YERVOY 3 mg/kg in MDX010-20, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported. In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-5 immune-mediated neuropathy occurred in 8 patients (2%); the sole fatality was due to complications of Guillain-Barré syndrome. Moderate Grade 2 immune-mediated neuropathy occurred in 1 patient (0.2%).

### **Immune-Mediated Endocrinopathies**

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY. Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediated. Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Withhold YERVOY in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. In patients receiving YERVOY 3 mg/kg in MDX010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 YERVOY-treated patients (1.8%). All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY. In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-4 immune-mediated endocrinopathies occurred in 39 patients (8%) and Grade 2 immune-mediated endocrinopathies occurred in 93 patients (20%). Of the 39 patients with Grade 3-4 immune-mediated endocrinopathies, 35 patients had hypopituitarism (associated with 1 or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 3 patients had hyperthyroidism, and 1 had

primary hypothyroidism. The median time to onset of Grade 3-4 immune-mediated endocrinopathy was 2.2 months (range: 2 days-8 months). Twenty-seven (69.2%) of the 39 patients were hospitalized for immune-mediated endocrinopathies. Of the 93 patients with Grade 2 immune-mediated endocrinopathy, 74 had primary hypopituitarism (associated with 1 or more secondary endocrinopathy, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 9 had primary hypothyroidism, 3 had hyperthyroidism, 3 had thyroiditis with hypo- or hyperthyroidism, 2 had hypogonadism, 1 had both hyperthyroidism and hypopituitarism, and 1 subject developed Graves' ophthalmopathy. The median time to onset of Grade 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days-19.3 months).

### Other Immune-Mediated Adverse Reactions

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions. Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. 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 YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss. Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody either before or after allogeneic hematopoietic stem cell transplantation (HSCT). Follow patients closely for evidence of GVHD and intervene promptly. Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody after allogeneic HSCT. In MDX010-20, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients: cytopenias, nephritis, pneumonitis, meningitis, pericarditis, uveitis, and iritis. In CA184-029, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients unless specified: cytopenias, eosinophilia (2.1%), pancreatitis (1.3%), meningitis, pneumonitis, sarcoidosis, pericarditis, uveitis, and fatal myocarditis. Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with <1% incidence unless specified: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, cytopenias (2.5%), and nephritis.

### Embryo-Fetal Toxicity

Based on its mechanism of action, 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 YERVOY and for 3 months after the last dose.

### Lactation

It is not known whether YERVOY is secreted in human milk. Advise women not to breastfeed during treatment with YERVOY and for 3 months after the last dose.

### Common Adverse Reactions

The most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%). The most common adverse reactions (≥5%) in patients who received YERVOY at 10 mg/kg were rash (50%), diarrhea (49%), fatigue (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%).

Please see U.S. Full Prescribing Information for [OPDIVO](#) and [YERVOY](#), including **Boxed WARNING regarding immune-mediated adverse reactions** for YERVOY.

### Checkmate Trials and Patient Populations

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

### **CABOMETYX® Important Safety Information**

#### Warnings and Precautions

**Hemorrhage:** Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

**Perforations and Fistulas:** Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

**Thrombotic Events:** CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

**Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure



regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

**Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

**Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Proteinuria:** Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

**Impaired Wound Healing:** Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

**Embryo-Fetal Toxicity:** CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

#### **Adverse Reactions**

The most commonly reported ( $\geq 25\%$ ) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.

#### **Drug Interactions**

**Strong CYP3A4 Inhibitors:** If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

**Strong CYP3A4 Inducers:** If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

#### **USE IN SPECIFIC POPULATIONS**

**Lactation:** Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

**Hepatic Impairment:** In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

**Please see accompanying full Prescribing Information:** <https://cabometyx.com/downloads/CABOMETYXUSPI.pdf>.

#### **About the Bristol Myers Squibb and Ono Pharmaceutical Collaboration**

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Bristol Myers Squibb expanded its territorial rights to develop and commercialize *Opdivo* globally, except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Ono and Bristol Myers Squibb further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

#### **About Bristol Myers Squibb**

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at [BMS.com](https://www.bms.com) or follow us on [LinkedIn](#), [Twitter](#), [YouTube](#), [Facebook](#) and [Instagram](#).

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol-Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol-Myers Squibb Company and Juno Therapeutics, a Bristol-Myers Squibb Company.

#### **About Exelixis**

Founded in 1994, Exelixis, Inc. (NASDAQ: EXEL) is a commercially successful, oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Following early work in model system genetics, we established a broad drug discovery and development platform that has served as the foundation for our continued efforts to bring new cancer therapies to patients in need. Our discovery efforts have resulted in four commercially available products, CABOMETYX<sup>®</sup> (cabozantinib), COMETRIQ<sup>®</sup> (cabozantinib), COTELLIC<sup>®</sup> (cobimetinib) and MINNEBRO<sup>®</sup> (esaxerenone), and we have entered into partnerships with leading

pharmaceutical companies to bring these important medicines to patients worldwide. Supported by revenues from our marketed products and collaborations, we are committed to prudently reinvesting in our business to maximize the potential of our pipeline. We are supplementing our existing therapeutic assets with targeted business development activities and internal drug discovery — all to deliver the next generation of Exelixa medicines and help patients recover stronger and live longer. Exelixa is a member of the Standard & Poor's (S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. For more information about Exelixa, please visit [www.exelixa.com](http://www.exelixa.com), follow @ExelixaInc on Twitter or like [Exelixa, Inc.](https://www.facebook.com/ExelixaInc) on Facebook.

### **Bristol Myers Squibb Cautionary Statement Regarding Forward-Looking Statements**

*This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that Opdivo in combination with CABOMETYX may not receive regulatory approval for the indication described in this release in the currently anticipated timeline or at all and, if approved, whether such combination treatment for such indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb's business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.*

### **Exelixa Cautionary Statement Regarding Forward-Looking Statements**

*This press release contains forward-looking statements, including, without limitation, statements related to: the possibility that the therapeutic combination of cabozantinib plus nivolumab may become an important new first-line option for RCC patients; the plan to present detailed findings from the CheckMate -9ER trial at an upcoming medical conference; the plan for BMS and Exelixa to work with global health authorities to seek marketing authorization for this therapeutic combination in the near future; and Exelixa's commitment to reinvest in our business to maximize the potential of our pipeline, including by supplementing our existing products with business development and internal drug discovery activities. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements are based upon Exelixa's current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: risks and uncertainties related to regulatory review and approval processes and BMS' and Exelixa's compliance with applicable legal and regulatory requirements; risks related to the potential failure of cabozantinib or nivolumab or the combination of these two drugs to demonstrate continued safety and efficacy in clinical testing; Exelixa's dependence on its relationships with its cabozantinib collaboration partners, including, the level of their investment in the resources necessary to successfully commercialize cabozantinib or nivolumab or the combination of these two drugs in the territories where approved; market acceptance of cabozantinib or nivolumab or the combination of these two drugs and the availability of coverage and reimbursement for these products or combinations; Exelixa's dependence on third-party vendors for the development, manufacture and supply of its products; the level of costs associated with Exelixa's commercialization, research and development and other activities; competition in business development activities and the inherent uncertainty of the drug discovery process; Exelixa's ability to protect its intellectual property rights; market competition; changes in economic and business conditions, including as a result of the global COVID-19 pandemic, and other factors discussed under the caption "Risk Factors" in Exelixa's annual report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 25, 2020, and in Exelixa's future filings with the SEC. The forward-looking statements made in this press release speak only as of the date of this press release. Exelixa expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Exelixa's expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based, except as required by law.*

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