U.S. Food and Drug Administration Accepts for Priority Review Applications for OPDIVO® (nivolumab) in Combination with CABOMETYX® (cabozantinib) in Advanced Renal Cell Carcinoma

October 19, 2020

U.S. Food and Drug Administration assigned a target action date of February 20, 2021

Applications based on pivotal Phase 3 CheckMate -9ER trial, which showed* OPDIVO *in combination with* CABOMETYX *improved overall survival, doubled median progression-free survival and objective response rate, and demonstrated a manageable safety profile

Results from CheckMate -9ER recently presented during a Presidential Symposium at the European Society for Medical Oncology Virtual Congress 2020

PRINCETON, N.J. & ALAMEDA, Calif.--(BUSINESS WIRE)--Oct. 19, 2020-- Bristol Myers Squibb (NYSE: BMY) and Exelixis, Inc. (NASDAQ: EXEL) today announced that the U.S. Food and Drug Administration (FDA) has accepted the supplemental Biologics License Application (sBLA) and supplemental New Drug Application (sNDA), respectively, for *OPDIVO*® (nivolumab) in combination with *CABOMETYX*® (cabozantinib) for patients with advanced renal cell carcinoma (RCC). The FDA granted Priority Review to both applications and assigned a Prescription Drug User Fee Act (PDUFA) goal date, or target action date, of February 20, 2021.

These filings were based on results from the Phase 3 CheckMate -9ER trial, which evaluated *OPDIVO* in combination with *CABOMETYX* in patients with previously untreated advanced RCC versus sunitinib. In CheckMate -9ER, *OPDIVO* in combination with *CABOMETYX* demonstrated significant improvements across all efficacy endpoints, including overall survival (OS), progression-free survival (PFS) and objective response rate (ORR), versus the comparator, sunitinib.

"We have witnessed practice-changing advancements in the treatment of renal cell carcinoma in recent years, but we recognize the importance of providing patients and physicians with additional options that can help them take control of the disease," said Mark Rutstein, vice president, development program lead, *OPDIVO*, Bristol Myers Squibb. "In the CheckMate -9ER trial, combining *OPDIVO* and *CABOMETYX*, two proven agents with strong clinical legacies in advanced renal cell carcinoma, led to superior efficacy across all endpoints. We look forward to working with the FDA to bring this potential treatment option to physicians and their patients who choose an immunotherapy plus tyrosine kinase inhibitor regimen."

"With their complementary mechanisms of action and evidence that *CABOMETYX* may promote a more immune-permissive environment, we believe there is opportunity for additive or synergistic effects with this potential combination regimen," said Gisela Schwab, M.D., president, product development and medical affairs and chief medical officer, Exelixis. "Based on strong supporting data from CheckMate -9ER, the acceptance of our application is important progress in our efforts to make *CABOMETYX* in combination with *OPDIVO* available to patients with advanced kidney cancer who need additional treatment options. We look forward to working with the FDA throughout the ongoing review process."

The combination of *OPDIVO* plus *CABOMETYX* was well tolerated, with a low rate of treatment-related discontinuations, and reflected the known safety profiles of the immunotherapy and tyrosine kinase inhibitor components in patients with previously untreated advanced RCC. In addition, patient-reported outcomes data from CheckMate -9ER showed that *OPDIVO* in combination with *CABOMETYX* was associated with statistically significant improvements in health-related quality of life at most time points versus sunitinib. On September 19, 2020, results from the trial were presented as a Proffered Paper during a Presidential Symposium at the European Society for Medical Oncology (ESMO) Virtual Congress 2020.

Bristol Myers Squibb and Exelixis thank the patients and investigators who were involved in the CheckMate -9ER clinical trial.

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 (RCC). A total of 651 patients (23% favorable risk, 58% intermediate risk, 20% poor risk; 25% PD-L1≥1%) were randomized to receive *OPDIVO* plus *CABOMETYX* (n=323) vs. sunitinib (n=328). 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 vs. 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. 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 patients' quality of life, 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 potential 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.

OPDIVO® INDICATIONS

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

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

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

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

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

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.

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

OPDIVO® IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions listed herein may not be inclusive of 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 at any time after starting or discontinuing YERVOY. Early identification and management are essential to ensure safe use of 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 before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue YERVOY depending on severity. In general, if YERVOY requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less followed by corticosteroid taper for at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroid therapy. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) of patients. In NSCLC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with OPDIVO 360 mg every 3 weeks in combination with YERVOY 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with OPDIVO in combination with YERVOY only. The incidence and severity of immune-mediated pneumonitis in patients with malignant pleural mesothelioma treated with OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks were similar to those occurring in NSCLC.

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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 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 trial of YERVOY 3 mg/kg, immune-mediated diarrhea/colitis occurred in 12% (62/511) of patients, including Grade 3-5 (7%).

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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 13% (51/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 20% (10/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 8% (10/119) of patients.

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

In a separate Phase 3 trial of YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 4.1% (21/511) of patients, including Grade 3-5 (1.6%).

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. Withhold for Grades 2, 3, or 4 endocrinopathies if not clinically stable. 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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 9% (36/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 4% (2/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hypophysitis occurred in 3.4% (4/119) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 5% (21/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 18% (9/49) 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 melanoma 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 HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (11/49) of patients. Hyperthyroidism occurred in 10% (5/49) 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 melanoma 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 trial of YERVOY 3 mg/kg, severe to life-threatening endocrinopathies occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies.

Immune-Mediated Nephritis and Renal Dysfunction

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

Immune-Mediated Skin and Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In

patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 22.6% (92/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 35% (17/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16% (90/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 14% (17/119) of patients.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous exfoliative rashes. Withhold YERVOY until specialist assessment for Grade 2 and permanently discontinue for Grade 3 or 4 exfoliative or bullous dermatologic conditions.

In a separate Phase 3 trial of YERVOY 3 mg/kg, immune-mediated rash occurred in 15% (76/511) of patients, including Grade 3-5 (2.5%).

Immune-Mediated Encephalitis

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

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. Dose modifications for YERVOY for adverse reactions that require management different from these general guidelines are summarized as follows. Withhold for Grade 2 and permanently discontinue YERVOY for Grade 3 or 4 neurological toxicities. Withhold for Grade 2 and permanently discontinue YERVOY for Grade 3 or 4 myocarditis. Permanently discontinue YERVOY for Grade 2, 3, or 4 ophthalmologic adverse reactions that do not improve to Grade 1 within 2 weeks while receiving topical therapy OR that require systemic 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, myasthenic syndrome, hemophagocytic lymphohistiocytosis (HLH), and autoimmune hemolytic anemia. 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: autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, nerve paresis, angiopathy, temporal arteritis, pancreatitis (1.3%), arthritis, polymyositis, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis, blepharitis, episcleritis, orbital myositis, scleritis, and solid organ transplant rejection. Some cases of ocular IMARs have been associated with retinal detachment.

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

Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. Severe infusion-related reactions can also occur with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions and interrupt or slow the rate of infusion in patients with mild or moderate infusion 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, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

In separate Phase 3 trials of YERVOY 3 mg/kg and 10 mg/kg, infusion-related reactions occurred in 2.9% (28/982).

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 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 PD-1 or CTLA-4 receptor 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 or YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

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

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

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

Lactation

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

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, 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 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 032, serious adverse reactions occurred in 45% of patients receiving OPDIVO (n=245). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, pneumonitis, pleural effusion, and dehydration. 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 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. 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 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 ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 040, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=154). The most frequent serious adverse reactions reported in ≥2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, pneumonia, and anemia. In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients. 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%).

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%),

decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), 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 032, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=245) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diarrhea (21%), constipation (20%), and cough (20%). In Checkmate 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO and 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 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 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 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough and dyspnea at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent, the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), 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 (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY (n=49), were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). In Attraction-3, the most common adverse reactions occurring in ≥20% of OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%).

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

Please see U.S. Full Prescribing Information for OPDIVO and 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 227–previously untreated metastatic non-small cell lung cancer, in combination with YERVOY; Checkmate 9LA–previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology; Checkmate 017–second-line treatment of metastatic squamous non-small cell lung cancer; Checkmate 057–second-line treatment of metastatic non-squamous non-small cell lung cancer; Checkmate 032–small cell lung cancer; Checkmate 743 – previously untreated unresectable malignant pleural mesothelioma, in combination with YERVOY; Checkmate 025–previously treated renal cell carcinoma; Checkmate 214–previously untreated renal cell carcinoma, in combination with YERVOY; Checkmate 205/039–classical Hodgkin lymphoma; Checkmate 141–recurrent or metastatic squamous cell carcinoma of the head and neck; Checkmate 275–urothelial carcinoma; Checkmate 142–MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY; Checkmate 040–hepatocellular carcinoma, as a single agent or in combination with YERVOY; Checkmate 238–adjuvant treatment of melanoma; Attraction-3—esophageal squamous cell carcinoma

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 (≥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 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® (cabozantinib),

COMETRIQ® (cabozantinib), COTELLIC® (cobimetinib) and MINNEBRO® (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 Exelixis medicines and help patients recover stronger and live longer. Exelixis 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 Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. 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 future study results will be consistent with the results to date, that Opdivo plus CABOMETYX may not receive regulatory approval for the indication described in this release 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.

Exelixis Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of the combination of CABOMETYX and Opdivo as a treatment for patients with advanced kidney cancer; the regulatory review process, including Exelixis' and BMS' plans to work with the FDA the during the FDA's review of Exelixis' and BMS' respective applications; and Exelixis' plans to reinvest in its business to maximize the potential of the company's pipeline, including through targeted business development activities and internal drug discovery. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and are based upon Exelixis' 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: complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere, including the risk that the FDA may not approve the combination of CABOMETYX and Opdivo as a treatment for advanced RCC in a timely fashion, if at all; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating the combination of CABOMETYX and Opdivo; Exelixis' dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for partnered compounds in new indications and their adherence to their obligations under relevant collaboration agreements; the continuing COVID-19 pandemic and its impact on Exelixis' product development and commercial activities; Exelixis' ability to protect its intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of CABOMETYX; changes in economic and business conditions; and other factors affecting Exelixis and its partners to obtain regulatory approval for cabozantinib in new indications discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 6, 2020, and in Exelixis' future filings with the SEC. All forward-looking statements in this press release are based on information available to Exelixis as of the date of this press release, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein, except as required by law.

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