Opdivo® (nivolumab) in Combination with CABOMETYX® (cabozantinib) Shows Durable Survival with Over Three Years of Follow-Up in the CheckMate -9ER Trial in First-Line Advanced Renal Cell Carcinoma

February 13, 2023

CORRECTED and REPLACING: Minor updates were made on April 24, 2023, to correct an error in the original data analysis impacting the blinded independent central reviewer (BICR)-assessed data points (PFS, ORR, and DoR). The safety and efficacy profile, including the OS data, was not affected and the data updates should not impact patient care.

The corrected version reads:

Data to be featured at ASCO GU 2023 demonstrate continued overall survival, progression-free survival and objective response rate benefits with* Opdivo *in combination with* CABOMETYX *compared to sunitinib, regardless of IMDC risk score

These three-year data – with a median follow-up of 44 months – from CheckMate -9ER represent the longest reported follow-up in any Phase 3 trial with an immunotherapy-tyrosine kinase inhibitor regimen in this population

In an exploratory biomarker analysis, median progression-free survival and overall survival were improved with the combination of* Opdivo *and* CABOMETYX *regardless of PD-L1 status

PRINCETON, N.J. & ALAMEDA, Calif.--(BUSINESS WIRE)--Feb. 13, 2023-- Bristol Myers Squibb (NYSE: BMY) and Exelixis, Inc. (NASDAQ: EXEL) today announced three-year (36.5 months minimum; 44.0 months median) follow-up results from the Phase 3 CheckMate -9ER trial, demonstrating sustained survival and response rate benefits with the combination of *Opdivo*® (nivolumab) and CABOMETYX® (cabozantinib) versus sunitinib in the first-line treatment of advanced renal cell carcinoma (RCC). Additionally, a biomarker analysis showed that improvements in median progression-free survival (PFS) and overall survival (OS) were sustained with the combination of *Opdivo* and CABOMETYX regardless of PD-L1 status. These updated results will be featured in one oral and one poster presentation at the American Society of Clinical Oncology (ASCO) 2023 Genitourinary Cancers Symposium from February 16-18, 2023.

“Despite the progress made through science and medicine, there remains a need for treatment options that can durably extend survival for patients with metastatic renal cell carcinoma, especially for those classified as higher risk,” said Mauricio Burotto, M.D., medical director, Bradford Hill Clinical Research Center, Santiago, Chile. “With these updated results from CheckMate -9ER, we’ve now seen nivolumab in combination with cabozantinib durably extend survival and sustain response benefits compared to sunitinib for over three years, regardless of patients’ risk classification. These results reinforce the importance of this immunotherapy-tyrosine kinase inhibitor regimen for patients and its potential to help change survival expectations for patients with this challenging cancer.”

Abstract #603: Nivolumab plus cabozantinib vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the phase 3 CheckMate -9ER trial (Burotto, et. al.)
With a median follow-up of 44.0 months (36.5 months minimum), *Opdivo* in combination with CABOMETYX (n=323) continued to show superior OS, PFS, objective response rate (ORR), duration of response (DoR) and complete response (CR) rates versus sunitinib (n=328). No new safety signals were seen with extended follow-up. Within the full study population:

- OS: Treatment with *Opdivo* in combination with CABOMETYX continued to show a 30% reduction in the risk of death (Hazard Ratio [HR] 0.70; 95% Confidence Interval [CI]: 0.56 to 0.87), and improvement in median OS vs. sunitinib (49.5 months vs. 35.5 months, respectively). Additionally, median OS improved by 11.8 months since the previous data cut at 32.9 months median follow-up.
- PFS: PFS benefits were sustained, with the combination continuing to double median PFS vs. sunitinib (16.6 months vs. 8.4 months, respectively; HR 0.59; 95% CI: 0.49 to 0.71).
- ORR and DoR: ORR benefits were maintained, with twice as many patients responding to *Opdivo* in combination with CABOMETYX vs. sunitinib (56% vs. 28%). Responses also continued to be more durable with the combination, with a median DoR of 22.1 months compared to 16.1 months with sunitinib.
- CR: CR rates were also sustained, with 13% of those treated with *Opdivo* in combination with CABOMETYX having a CR vs. 5% of those treated with sunitinib.
- Safety: 97% of patients treated with *Opdivo* in combination with CABOMETYX experienced a treatment-related adverse event (TRAE) of any grade compared to 93% of patients treated with sunitinib; 67% vs. 55% had a grade ≥3 TRAE, respectively.

Results were also assessed by the following International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores: favorable, intermediate, intermediate/poor and poor. Benefits were seen with *Opdivo* in combination with CABOMETYX across all efficacy measures (OS, PFS, ORR and CR), regardless of IMDC risk.

Abstract #608: Biomarker analysis from the phase 3 CheckMate 9ER trial of nivolumab + cabozantinib v sunitinib for advanced renal cell carcinoma (aRCC) (Choueiri, et. al.)
In an exploratory post-hoc analysis from CheckMate -9ER with 44.0 months median follow-up, improvements were observed in both median PFS and OS with *Opdivo* in combination with CABOMETYX regardless of PD-L1 status. PFS and OS were evaluated by tumor PD-L1 expression (<1% or ≥1%), CD8% (low, medium, high by tertiles), and CD8 topology phenotype (cold, excluded, inflamed), and assessed for association using Kaplan-Meier (KM) methods with log-rank test (PD-L1 and CD8), and Cox proportional hazard (Cox PH) models (CD8). Biomarkers previously found to be predictive of anti-PD-L1 + anti-VEGF outcomes, including established gene

expression signatures, were not necessarily predictive of efficacy with anti-PD-1 + anti-VEGF targeted therapy, suggesting that key determinants of response to anti-PD-1 vs. anti-PD-L1 therapies may differ.

“We have a strong heritage of bringing immunotherapy-based combinations to patients with advanced renal cell carcinoma and transforming patient outcomes with *Opdivo*-based combinations across several cancer types,” said Dana Walker, M.D., M.S.C.E., vice president, development program lead, genitourinary cancers, Bristol Myers Squibb. “The updated data from CheckMate -9ER further reinforce the use of *Opdivo* in combination with CABOMETYX for the first-line treatment of patients with advanced renal cell carcinoma. We remain committed to collaboration across the scientific community and our ongoing exploration of combination approaches with our proven cancer agents in the pursuit of solutions that may help improve long-term outcomes for as many patients as possible.”

“With forty-four months median follow-up, the compelling survival benefit further reinforces the value of the CABOMETYX and *Opdivo* combination regimen as a first-line option for patients with advanced kidney cancer,” said Vicki L. Goodman, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. “We are pleased to share these long-term findings at ASCO GU and remain steadfast in our longstanding commitment to improving outcomes for patients living with advanced kidney cancer.”

Bristol Myers Squibb and Exelixis thank the patients and investigators 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, Inc., Ipsen Pharma SAS 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 431,000 new cases and 179,000 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. At diagnosis, up to 30% of patients present with advanced or metastatic RCC.

Bristol Myers Squibb: Creating a Better Future for People with Cancer
Bristol Myers Squibb is inspired by a single vision — transforming patients’ lives through science. The goal of the company’s cancer research is to deliver medicines that offer each patient a better, healthier life and to make cure a possibility. Building on a legacy across a broad range of cancers that have changed survival expectations for many, Bristol Myers Squibb researchers are exploring new frontiers in personalized medicine, and through innovative digital platforms, are turning data into insights that sharpen their focus. Deep scientific expertise, cutting-edge capabilities and discovery platforms enable the company to look at cancer from every angle. Cancer can have a relentless grasp on many parts of a patient’s life, and Bristol Myers Squibb is committed to taking actions to address all aspects of care, from diagnosis to survivorship. Because as a leader in cancer care, Bristol Myers Squibb is working to empower all people with cancer to have a better future.

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 September 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.

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

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

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

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

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

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

OPDIVO® (nivolumab), in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

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

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

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

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

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

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

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

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

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

OPDIVO IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune- mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

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

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

Immune-Mediated Colitis

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

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune- mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%).

OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. In patients receiving OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients.

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). In patients receiving OPDIVO and cabozantinib, adrenal insufficiency occurred in 4.7% (15/320) of patients, including Grade 3 (2.2%) and Grade 2 (1.9%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, diabetes occurred in 2.7% (15/666) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

Immune-Mediated Nephritis with Renal Dysfunction

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

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non- bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4)

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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

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

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

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

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

Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. In Checkmate 816, serious adverse reactions occurred in 30% of patients (n=176) who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy. In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 057, fatal adverse reactions occurred; these included events of infection (7 patients, including one case of Pneumocystis jirovecii pneumonia), pulmonary embolism (4 patients), and limbic encephalitis (1 patient). In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis. In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion- related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 274, serious adverse reactions occurred in 30% of patients receiving OPDIVO (n=351). The most frequent serious adverse reaction reported in ≥2% of patients receiving OPDIVO was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis. In Attraction-3, serious adverse reactions occurred in 38% of patients receiving OPDIVO (n=209). Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease, and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic

shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%). In Checkmate 577, serious adverse reactions occurred in 33% of patients receiving OPDIVO (n=532). A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal reaction of myocardial infarction occurred in one patient who received OPDIVO. In Checkmate 648, serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy (n=310). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury. In Checkmate 648, serious adverse reactions occurred in 69% of patients receiving OPDIVO in combination with YERVOY (n=322). The most frequent serious adverse reactions reported in ≥2% who received OPDIVO in combination with YERVOY were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with YERVOY; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome. In Checkmate 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). In Checkmate 816, the most common (>20%) adverse reactions in the OPDIVO plus chemotherapy arm (n=176) were nausea (38%), constipation (34%), fatigue (26%), decreased appetite (20%), and rash (20%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY were fatigue (43%), musculoskeletal pain (38%), rash (34%), diarrhea (32%), dyspnea (27%), nausea (24%), decreased appetite (24%), cough (23%), and pruritus (21%). In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%). In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%) and upper respiratory tract infection (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough (14%) and dyspnea (14%) at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 274, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=351) were rash (36%), fatigue (36%), diarrhea (30%), pruritus (30%), musculoskeletal pain (28%), and urinary tract infection (22%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent (n=74), the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), cough (26%), pyrexia (24%), rash (23%), constipation (20%), and upper respiratory tract infection (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY (n=49), were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%). In Attraction-3, the most common adverse reactions (≥20%) in OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%). In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=532) were fatigue (34%), diarrhea (29%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%). In Checkmate 648, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=310) were nausea (65%), decreased appetite (51%), fatigue (47%), constipation (44%), stomatitis (44%), diarrhea (29%), and vomiting (23%). In Checkmate 648, the most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with YERVOY were rash (31%), fatigue (28%), pyrexia (23%), nausea (22%), diarrhea (22%), and constipation (20%). In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%).

Please see US Full Prescribing Information for OPDIVO and YERVOY.

Clinical Trials and Patient Populations

Checkmate 037–previously treated metastatic melanoma; Checkmate 066—previously untreated metastatic melanoma; Checkmate 067–previously untreated metastatic melanoma, as a single agent or in combination with YERVOY; Checkmate 238–adjuvant treatment of melanoma; Checkmate 816–neoadjuvant non-small cell lung cancer, in combination with platinum-doublet chemotherapy; Checkmate 227—previously untreated metastatic non-small cell lung cancer, in combination with YERVOY; Checkmate 9LA–previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology; Checkmate 017–second-line treatment of metastatic squamous non-small cell lung cancer; Checkmate 057–second-line treatment of metastatic non-squamous non-small cell lung cancer; Checkmate 743–previously untreated unresectable malignant pleural mesothelioma, in combination with YERVOY; Checkmate 214–previously untreated renal cell carcinoma, in combination with YERVOY; Checkmate 9ER–previously untreated renal cell carcinoma, in combination with cabozantinib; Checkmate 025–previously treated renal cell carcinoma; Checkmate 205/039–classical Hodgkin lymphoma; Checkmate 141–recurrent or metastatic squamous cell carcinoma of the head and neck; Checkmate 275–previously treated advanced or metastatic urothelial carcinoma; Checkmate 274–adjuvant treatment of urothelial carcinoma; Checkmate 142– MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY; Checkmate 142–MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY; Checkmate 040–hepatocellular carcinoma, in combination with YERVOY; Attraction-3–esophageal squamous cell carcinoma; Checkmate 577–adjuvant treatment of esophageal or gastroesophageal junction cancer; Checkmate 648—previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma; Checkmate 648—previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma; Checkmate 649–previously untreated advanced metastatic gastric cancer, gastroesophageal junction and esophageal adenocarcinoma.

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced renal cell carcinoma (RCC); for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib; for patients with advanced RCC as a first-line treatment in combination with nivolumab; and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. CABOMETYX tablets have also received regulatory approvals in the European Union 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 U.S. and Japan. In 2017, Exelixis granted exclusive rights to Takeda 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 U.S.

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, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, 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 events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% 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. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% 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.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. 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, resume at a reduced dose.

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. 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.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

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 common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

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. Avoid CABOMETYX in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information https://www.cabometyx.com/downloads/CABOMETYXUSPI.pdf

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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.

About Exelixis
Exelixis is a globally ambitious oncology company innovating next-generation medicines and regimens at the forefront of cancer care. Powered by bi-coastal centers of discovery and development excellence, we are rapidly evolving our product portfolio to target an expanding range of tumor types and indications with our clinically differentiated pipeline of small molecules, antibody-drug conjugates and other biotherapeutics. This comprehensive approach harnesses decades of robust investment in our science and partnerships to advance our investigational programs and extend the impact of our flagship commercial product, CABOMETYX® (cabozantinib). Exelixis is driven by a bold scientific pursuit to create transformational treatments that give more patients hope for the future. For information about the company and its mission to help cancer patients recover stronger and live longer, visit www.exelixis.com, follow @ExelixisInc on Twitter, like Exelixis, Inc. on Facebook and follow Exelixis on LinkedIn.

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 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 may not be consistent with the results to date, that Opdivo® (nivolumab) in combination with CABOMETYX® (cabozantinib) will be commercially successful, that any marketing approvals, if granted, may have significant limitations on their use, and, that continued approval of such combination treatment for such indication described in this release may be contingent upon verification and description of clinical benefit in additional confirmatory trials. 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, 2021, 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 presentation of updated results from the CheckMate -9ER trial during oral and poster sessions at ASCO GU 2023; the therapeutic potential of cabozantinib in combination with nivolumab to help change survival expectations for patients with advanced RCC; Exelixis' longstanding commitment to improving outcomes for patients living with advanced RCC; and Exelixis' scientific pursuit to create transformational treatments that give more patients hope for the future. 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: the availability of data at the referenced times; complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' and Bristol Myers Squibb's continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib in combination with nivolumab to demonstrate safety and/or efficacy in future clinical testing; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; the costs of conducting clinical trials; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; Exelixis' and Bristol Myers Squibb's ability to protect their respective intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of CABOMETYX; changes in economic and business conditions, including as a result of the COVID-19 pandemic and other global events; and other factors affecting Exelixis and its development programs discussed under the caption "Risk Factors" in Exelixis' Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 7, 2023, 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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