China National Drug Administration Approves Country’s First Immuno-Oncology Agent, Opdivo (nivolumab injection), for Previously Treated Non-Small Cell Lung Cancer (NSCLC)

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The first and only PD-1 inhibitor approved in China opens a new era of Immuno-Oncology treatment for a type of lung cancer

Opdivo demonstrated superior overall survival versus docetaxel in patients with previously treated NSCLC, regardless of PD-L1 expression and tumor histology, in a Phase 3 trial

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) announced today that the China National Drug Administration (CNDA) has approved Opdivo (nivolumab injection) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior platinum-based chemotherapy in adult patients without EGFR or ALK genomic tumor aberrations. This is China’s first and only PD-1 inhibitor and is the only Immuno-Oncology (I-O) agent to demonstrate a survival benefit compared with chemotherapy, based on data from the pivotal Phase 3 CheckMate -078 trial, in which 90% of the patients enrolled were Chinese.

“Lung cancer is a major public health issue in China, representing the highest incidence and mortality among all cancers in the country,” said Professor Yi-Long Wu, a tenured director of Guangdong General Hospital and the chair of the Chinese Thoracic Oncology Group. “With most lung cancer patients already at an advanced stage when diagnosed, prolonging survival is an important goal. The approval of Opdivo as the first I-O agent in China is a significant therapeutic advance and is great news for patients and clinicians alike, offering for the first time an I-O treatment option that is proven to extend survival in predominantly Chinese patients with previously treated NSCLC.”

The approval is based on results from the Phase 3 CheckMate -078 trial of Opdivo versus chemotherapy among patients with previously treated NSCLC, findings from which were presented at the American Association for Cancer Research Annual Meeting in April 2018. In November 2017, the trial was stopped early because the independent Data Monitoring Committee concluded that Opdivo demonstrated superior overall survival compared with chemotherapy. The application later received priority review by the Center for Drug Evaluation in China.

Murdo Gordon, executive vice president and chief commercial officer, Bristol-Myers Squibb, commented, “With approvals in more than 60 countries, Opdivo is a global standard of care for previously treated NSCLC, and we are proud to bring this foundational I-O treatment option to patients and physicians in China. We look forward to continuing to work together with the CNDA to usher in additional healthcare innovations in China, with our shared commitment to moving quickly to help patients.”

InCheckMate -078, Opdivo reduced the risk of death by 32% versus chemotherapy, the primary endpoint (HR 0.68; 97.7% CI: 0.52 to 0.90; p=0.0006), in patients with previously treated NSCLC. Both efficacy and safety of Opdivo in this patient population were consistent with the results of the landmark global CheckMate -017 and -057 studies. In CheckMate -078, Grade 3-4 treatment-related adverse events (TRAEs) occurred less frequently with Opdivo versus docetaxel (10% vs. 48%). Discontinuations due to Grade 3-4 TRAEs were also less frequent with Opdivo (3%) than with docetaxel (5%).

“We are thrilled to be able to bring this proven treatment, Opdivo, which has demonstrated superior overall survival versus chemotherapy in previously treated NSCLC patients in China, and are committed to working with stakeholders to ensure patients can quickly access Opdivo,” said Fouad Namouni, M.D., head of development, Oncology, Bristol-Myers Squibb. “With more than 7,500 cancer deaths per day estimated in China, we will continue to work with urgency to integrate the unmet treatment needs of Chinese patients in our ongoing I-O global development program, with the goal of bringing them innovative therapies as quickly as possible.”

About CheckMate -078
CheckMate -078 is a Phase 3, multinational, randomized study comparing Opdivo with docetaxel in the treatment of patients with Stage IIIb/IV NSCLC whose disease has progressed after platinum-based doublet chemotherapy. The study was conducted primarily in China, with additional study sites in Hong Kong, Russia, and Singapore. The trial randomized 504 patients (451 from China, 45 from Russia, 8 from Singapore) without EGFR mutations and with both squamous and non-squamous NSCLC, across PD-L1 expression status of <1% and ≥1%, to receive either Opdivo 3 mg/kg intravenously every two weeks (N=338) or docetaxel 75 mg/m² intravenously every three weeks (N=166) until documented disease progression or unacceptable toxicity.

The primary endpoint was overall survival (OS), including OS consistency observed with the global CheckMate -017 and CheckMate -057 studies. Secondary endpoints included objective response rate (ORR), progression-free survival, time to treatment failure, efficacy across subgroups, rates of treatment-related adverse events, and rate of disease-related symptom deterioration, as measured by the Lung Cancer Symptom Scale.

Minimum follow-up was 8.8 months. Median OS was 12.0 months in the Opdivo arm and 9.6 months in the chemotherapy arm (HR 0.68; 95% CI: 0.52 to 0.90; p=0.006). Improved OS with Opdivo versus docetaxel was observed in patients with squamous (HR 0.61; 95% CI: 0.42 to 0.89) and non-squamous (HR 0.76; 95% CI: 0.56 to 1.04) tumor histology, and across all pre-defined subgroups based on tumor PD-L1 expression level. The hazard ratios in patients with tumor PD-L1 expression ≥1% and <1% were 0.62 (95% CI: 0.45 to 0.87) and 0.75 (95% CI: 0.52 to 1.09), respectively. The ORR was 17% with Opdivo versus 4% with docetaxel. Median duration of response was not reached in the Opdivo arm versus 5.3 months in the docetaxel arm. Opdivo decreased risk of disease progression by 23% versus docetaxel (HR 0.77; 95% CI: 0.62 to 0.95; p=0.0147).

About Lung Cancer

Lung cancer is the leading cause of cancer deaths globally, resulting in nearly 1.7 million deaths each year, according to the World Health Organization. Non-small cell lung cancer (NSCLC) is one of the most common types of the disease and accounts for approximately 85% of diagnoses. There are approximately 781,000 new cases of lung cancer diagnosed in China each year, equaling approximately 15 new cases every 10 minutes. This number continues to rise, with more than 800,000 new cases and 700,000 new deaths projected by 2020. Survival rates vary depending on the stage and type of the cancer when diagnosed, with the five-year survival rate lower than 5%. For patients with advanced squamous cell lung cancer and non-squamous NSCLC without any known driver genetic mutation, treatment measures are quite limited. Therefore, long-term survival is the most urgent need of those patients.

Bristol-Myers Squibb & Immuno-Oncology: Advancing Oncology Research

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational medicines, including Immuno-Oncology (I-O) therapeutic approaches, for hard-to-treat cancers that could potentially improve outcomes for these patients.

We are leading the integrated scientific understanding of both tumor cell and immune system pathways, through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 50 types of cancers with 24 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance I-O/I-O, I-O/chemotherapy, I-O/targeted therapies and I-O/radiation therapies across multiple tumors and potentially deliver the next wave of therapies with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and how a patient’s tumor biology can be used as a guide for treatment decisions through their journey.

We understand making the promise of transformational medicines like I-O therapies a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

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 enrolled more than 25,000 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 60 countries, including the United States, the European Union and Japan. 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.

U.S. FDA-APPROVED INDICATIONS FOR OPDIVO®

OPDVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or
metastatic melanoma.

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

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

OPDIVO® (10 mg/mL) is an injection for intravenous (IV) use.

IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

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

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

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

Immune-Mediated Pneumonitis

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

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

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

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

**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 >3 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 13% (51/407) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (30/460) of patients.

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

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

**Immune-Mediated Neuropathies**

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

**Immune-Mediated Endocrinopathies**

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

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 9% (36/407) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 3% (21/717) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (41/547) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving this dose of OPDIVO with YERVOY. In 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 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 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 patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 1.5% (6/407) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. 6 of the 9 patients were hospitalized for severe endocrinopathies.

**Immune-Mediated Nephritis and Renal Dysfunction**

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients. In 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.
Immune-Mediated Skin Adverse Reactions and Dermatitis

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 22.6% (92/407) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16.6% (91/547) of patients.

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

Immune-Mediated Encephalitis

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

Other Immune-Mediated Adverse Reactions

Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following were among the most significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pericarditis, pancreatitis, facial and abducens nerve paresis, demyelination, polyneuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoïdosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

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

Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate study in which patients received OPDIVO monotherapy as a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In patients receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients.

Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT without discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or 4 acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Embryo-Fetal Toxicity

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

Lactation
It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from an OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue breastfeeding during treatment with YERVOY and for 3 months following the final dose.

**Serious Adverse Reactions**

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in ≥2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO. 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 (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) 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 2.6%), colitis (10% and 1.6%), and pyrexia (15% and 6%). In Checkmate 017 and 057, serious (10%) and reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY and in 43% of patients receiving sunitinib. The most frequent serious adverse reactions reported in at least 2% of patients were diarrhea, pyrexia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. In Checkmate 205 and 039, adverse reactions leading to permanent 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 at least 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 at least 2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

**Common Adverse Reactions**

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reaction (≥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 (59%), rash (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). 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 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO vs sunitinib (n=535) were fatigue (58% vs 69%), rash (39% vs 25%), diarrhea (38% vs 58%), musculoskeletal pain (37% vs 40%), pruritus (33% vs 11%), nausea (30% vs 43%), cough (28% vs 25%), pyrexia (25% vs 17%), arthralgia (23% vs 16%), and decreased appetite (21% vs 29%). 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 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 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%). The most common adverse reactions (≥20%) in patients who received OPDIVO as a single agent were fatigue, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain.

In a separate Phase 3 study 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%).

**Checkmate Trials and Patient Populations**
Checkmate 067—advanced melanoma alone or in combination with YERVOY® (ipilimumab); Checkmate 037 and 066—advanced melanoma; Checkmate 017—squamous non-small cell lung cancer (NSCLC); Checkmate 057—non-squamous NSCLC; Checkmate 025—renal cell carcinoma; Checkmate 205/039—classical Hodgkin lymphoma; Checkmate 141—squamous cell carcinoma of the head and neck; Checkmate 275—urothelial carcinoma; Checkmate 040—hepatocellular carcinoma, Checkmate 238—adjuvant treatment of melanoma.

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY.

About the Bristol-Myers Squibb and Ono Pharmaceutical Co., Ltd. Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Ltd. (Ono), 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, Bristol-Myers Squibb and Ono 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 and Facebook.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2017 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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#MEDIA: #BMY receives CNDA approval of the first #ImmunoOncology agent in China