

November 25, 2015

**Bristol-Myers Squibb Receives FDA Approval for Opdivo (nivolumab),
the Only Treatment to Deliver Significant Overall Survival
in Advanced Renal Cell Carcinoma vs. a Standard of Care,
in Patients Who Have Received Prior Anti-Angiogenic Therapy**

(PRINCETON, NJ, November 23, 2015) – Bristol-Myers Squibb Company (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) injection, for intravenous use, for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

In USA, Opdivo was approved under accelerated approval for the treatment of unresectable or metastatic melanoma and disease progression following Yervoy and, if BRAF V600 mutation positive, a BRAF inhibitor in December 2014 and approved for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy in March 2015. Also, Opdivo in combination with Yervoy for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma received the approval in October 2015. Opdivo received expanded FDA approval in previously-treated metastatic non-small cell lung cancer in the same month. In EU, Opdivo was approved for the treatment of advanced (unresectable or metastatic) melanoma in adults regardless of BRAF status in June 2015. European Commission approved Nivolumab BMS for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in July 2015.

Also, BMS has a robust clinical development program in a variety of tumor types overseas, including: Renal Cell Carcinoma (RCC), Head and Neck Cancer, Blood Cancer, Glioblastoma, Colorectal Cancer, Pancreatic Cancer, Gastric Cancer, Hepatocellular Carcinoma, Triple-Negative Breast Cancer, Small-Cell Lung Cancer, Urothelial Cancer. In Japan, ONO launched it for the treatment of unresectable melanoma in September 2014. Also, ONO is conducting clinical development programs including RCC, NSCLC, Head and Neck Cancer, Gastric Cancer, Esophageal Cancer, Hepatocellular Carcinoma, Hodgkin Lymphoma, Urothelial Cancer and Glioblastoma.

Attached from the following page is the press release made by BMS for your information.

Contact
ONO PHARMACEUTICAL CO., LTD.
Corporate Communications
public_relations@ono.co.jp



Bristol-Myers Squibb Receives FDA Approval for *Opdivo* (nivolumab), the Only Treatment to Deliver Significant Overall Survival in Advanced Renal Cell Carcinoma vs. a Standard of Care, in Patients Who Have Received Prior Anti-Angiogenic Therapy¹

The first and only PD-1 inhibitor approved based on a demonstrated OS benefit in patients with advanced RCC who have received prior anti-angiogenic therapy¹

*Approval based on CheckMate -025, which demonstrated median OS benefit of 25 months (95% CI: 21.7-NE) for *Opdivo* vs. 19.6 months (95% CI: 17.6-23.1) for everolimus (HR: 0.73; [95% CI: 0.60-0.89; p=0.0018])^{1,2}*

*With this fifth approval for *Opdivo* in 12 months, in a third distinct tumor type, more patients with cancer now have access to an Immuno-Oncology treatment option¹*

(PRINCETON, NJ, November 23, 2015) – [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved *Opdivo* (nivolumab) injection, for intravenous use, for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.¹ Today’s announcement marks the approval of the first and only PD-1 inhibitor to deliver significant overall survival (OS) in patients with advanced RCC who have received prior anti-angiogenic therapy.¹ In the CheckMate -025 trial, patients treated with *Opdivo* achieved a median OS of 25 months (95% CI: 21.7-not estimable [NE]) versus 19.6 months (95% CI: 17.6-23.1) for everolimus, a current standard of care (SOC) in this patient population (hazard ratio [HR]: 0.73; [95% CI: 0.60-0.89; p=0.0018]), based on a prespecified interim analysis.^{1,2} In the study, the safety profile was consistent with prior *Opdivo* studies.²

“This is the fifth approval for *Opdivo* across three distinct tumor types. This latest approval reflects our commitment to delivering on our promise to provide cancer patients with a potential for long-term survival,” said [Francis Cuss](#), MB BChir, FRCP, executive vice president and chief scientific officer at Bristol-Myers Squibb. “We believe our pioneering approach to Immuno-Oncology is driving change in how cancer may be treated.”

Opdivo is associated with immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryofetal toxicity. Please see the Important Safety Information section below.¹

The U.S. approval was based on data from CheckMate -025, an open-label, randomized Phase 3 study which demonstrated a median OS benefit of 25 months (95% CI: 21.7-NE) compared with 19.6 months (95% CI: 17.6-23.1) for everolimus (HR: 0.73; [95% CI: 0.60-0.89; p=0.0018]).^{1,2} This is the first time an immune checkpoint inhibitor has delivered a significant survival benefit in this patient population.¹ On September 16, 2015, the FDA granted Breakthrough Therapy Designation to *Opdivo* for advanced RCC patients treated with prior anti-angiogenic therapy, also based on positive results from the CheckMate -025 study, reinforcing the unmet need in the treatment of RCC.²

“As an Immuno-Oncology agent that works directly with the body’s immune system, *Opdivo* offers a new approach for physicians to use when treating patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy,” continued Cuss. “For the first time, these patients have a PD-1 inhibitor treatment option, which has the potential to provide an unprecedented survival advantage compared to a standard of care.”

Proven Significant Overall Survival vs. a Standard of Care

CheckMate -025 is a landmark, open-label, randomized Phase 3 study, evaluating *Opdivo* compared to an active comparator (everolimus) in patients with advanced RCC who have received prior anti-angiogenic therapy.^{1,2} Clinical results from CheckMate -025 were recently presented at the 2015 European Cancer Congress with simultaneous publication in *The New England Journal of Medicine*.²

In CheckMate -025, 821 patients were randomized to receive *Opdivo* (3 mg/kg administered intravenously every two weeks; n=410) compared to a SOC (everolimus, 10 mg administered orally daily; n=411).^{1,2} The primary endpoint was OS.^{1,2} Objective response rate (ORR) was evaluated as a secondary endpoint.^{1,2} The prespecified interim analysis was conducted when 398 events were observed (70% of the planned number of events for final analysis).¹ In this trial, *Opdivo* demonstrated a median OS of 25 months (95% CI: 21.7-NE) versus 19.6 months (95% CI: 17.6-23.1) for everolimus (HR: 0.73; [95% CI: 0.60-0.89; p=0.0018]), offering a 5.4 month survival benefit.¹ With *Opdivo*, the OS benefit was observed independent of PD-L1 expression.¹ In addition to improving survival, *Opdivo* demonstrated a superior ORR compared to everolimus (21.5%; 95% CI: 17.6-25.80 vs. 3.9%; 95% CI: 2.2-6.2)

with a higher median duration of response (23.0 months; 95% CI: 12.0-NE vs. 13.7 months; 95% CI: 8.3-21.9).¹

“Results from CheckMate -025 mark the first time an Immuno-Oncology treatment has demonstrated a survival advantage in patients with advanced renal cell carcinoma compared to a standard of care in this population,” said Robert J. Motzer, M.D., medical oncologist, Memorial Sloan Kettering Cancer Center. “For patients with advanced renal cell carcinoma, treatment options are limited and new approaches that extend survival are desperately needed. With the FDA approval of *Opdivo*, the kidney cancer community is now a step closer toward achieving long-term survival, which has remained elusive for many patients. This represents a true shift in our treatment paradigm.”

While the treatment landscape for RCC has improved over the last decade, patients are in need of new treatment options that demonstrate longer-term effects and overall survival benefits.³

“This approval of *Opdivo* represents a major milestone for the kidney cancer community,” said William P. Bro, chief executive officer and patient coordinator, Kidney Cancer Association. “We thank Bristol-Myers Squibb and the FDA for working swiftly to bring this important new treatment option and potential for extended survival to patients.”

The safety profile of *Opdivo* in CheckMate -025 was consistent with prior studies.² Serious adverse events occurred in 47% of patients receiving *Opdivo*.¹ The most frequent serious adverse reactions reported in at least 2% of patients receiving *Opdivo* were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.¹ In the study, the most common adverse reactions ($\geq 20\%$) reported in patients receiving *Opdivo* versus everolimus were asthenic conditions (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%).¹

About Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the most common type of kidney cancer in the U.S., accounting for approximately 9 out of 10 kidney cancers.³ An estimated 61,560 new cases of kidney cancer will be diagnosed in 2015 in the U.S., and the disease is more common in men than women.³ Clear-cell RCC is the most prevalent type of RCC, which includes 70% of all

cases.³ Approximately 14,000 people will die from kidney cancer in the U.S. in 2015 and the five-year survival rate for patients diagnosed with advanced kidney cancer is 8%.³

Leading Immuno-Oncology Development in Renal Cell Carcinoma

Bristol-Myers Squibb is a pioneer in the field of cancer research and treatment known as Immuno-Oncology, which involves agents whose primary mechanism is to work directly with the body's immune system to fight cancer.

Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor, and works by targeting the immune system through the PD-1 immune checkpoint pathway.¹ Targeting the immune system through this pathway is now recognized as a new approach to RCC treatment.³

Bristol-Myers Squibb has a broad, global development program to study *Opdivo* in multiple tumor types consisting of more than 50 trials – as a monotherapy or in combination with other therapies – in which more than 8,000 patients have been enrolled worldwide.

About Bristol-Myers Squibb's Patient Support Programs

Bristol-Myers Squibb remains committed to helping patients access our medicines. For support and assistance, patients and physicians may call 1-855-OPDIVO-1. This number offers one-stop access to a range of support services for patients and healthcare professionals alike.

About Bristol-Myers Squibb's Access Support

Bristol-Myers Squibb is committed to helping patients access *Opdivo* and offers BMS Access Support[®] to support patients and providers in gaining access. BMS Access Support, the Bristol-Myers Squibb Reimbursement Services program, is designed to support access to BMS medicines and expedite time to therapy through reimbursement support including Benefit Investigations, Prior Authorization Facilitation, Appeals Assistance, and assistance for patient out-of-pocket costs. BMS Access Support assists patients and providers throughout the treatment journey – whether it is at initial diagnosis or in support of transition from a clinical trial. More information about our reimbursement support services can be obtained by calling 1-800-861-0048 or by visiting www.bmsaccesssupport.com. For healthcare providers seeking specific reimbursement information, please visit the BMS Access Support Product section by visiting www.bmsaccesssupportopdivo.com.

INDICATIONS

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

OPDIVO[®] as a single agent is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. 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 confirmatory trials.

OPDIVO[®], in combination with ipilimumab, is indicated for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. 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 confirmatory trials.

OPDIVO[®] 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[®].

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), adrenocorticotrophic 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

Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred with OPDIVO. In Checkmate 069, there were six additional patients who died without resolution of abnormal respiratory findings. Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In Checkmate 037, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis occurred in 2.2% (6/268) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=5). In Checkmate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients: Grade 3 (n=5), Grade 2 (n=2), and Grade 1 (n=3). In Checkmate 025, pneumonitis, including interstitial lung disease, occurred in 5.2% (21/406) of patients receiving OPDIVO and 18.4% (73/397) of patients receiving everolimus. Immune-mediated pneumonitis occurred in 4.4% (18/406) of patients receiving OPDIVO: Grade 4 (n=1), Grade 3 (n=4), Grade 2 (n=12), and Grade 1 (n=1). In Checkmate 069, pneumonitis, including interstitial lung disease, occurred in 10% (9/94) of patients receiving OPDIVO in combination with YERVOY and 2.2% (1/46) of patients receiving YERVOY. Immune-mediated pneumonitis occurred in 6% (6/94) of patients receiving OPDIVO in combination with YERVOY: Grade 5 (n=1), Grade 3 (n=2) and Grade 2 (n=3).

Immune-Mediated Colitis

Immune-mediated colitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. As a single agent, withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon restarting OPDIVO. In combination with YERVOY, withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis upon restarting OPDIVO. In Checkmate 037, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis occurred in 2.2% (6/268) of patients receiving OPDIVO; Grade 3 (n=5) and Grade 2 (n=1). In Checkmate 057, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: Grade 3 (n=3), Grade 2 (n=2), and Grade 1 (n=2). In Checkmate 025, diarrhea or colitis occurred in 25% (100/406) of patients receiving OPDIVO and 32% (126/397) of patients receiving everolimus. Immune-mediated diarrhea or colitis occurred in 3.2% (13/406) of patients receiving OPDIVO: Grade 3 (n=5), Grade 2 (n=7), and Grade 1 (n=1). In Checkmate 069, diarrhea or colitis occurred in 57% (54/94) of patients receiving OPDIVO in combination with YERVOY and 46% (21/46) of patients receiving YERVOY. Immune-mediated colitis occurred in 33% (31/94) of patients receiving OPDIVO in combination with YERVOY: Grade 4 (n=1), Grade 3 (n=16), Grade 2 (n=9), and Grade 1 (n=5).

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

Immune-mediated hepatitis can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In Checkmate 037, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs 12%), alkaline phosphatase (22% vs 13%), ALT (16% vs 5%), and total bilirubin (9% vs 0). Immune-mediated hepatitis occurred in 1.1% (3/268) of patients receiving OPDIVO; Grade 3 (n=2) and Grade 2 (n=1). In Checkmate 057, one patient (0.3%) developed immune-mediated hepatitis. In Checkmate 025, there was an increased incidence of liver test abnormalities compared to baseline in AST (33% vs 39%), alkaline phosphatase (32% vs 32%), ALT (22% vs 31%), and total bilirubin (9% vs 3%) in the OPDIVO-treated and everolimus-treated groups, respectively. Immune-mediated hepatitis requiring systemic immunosuppression occurred in 1.5% (6/406) of patients receiving OPDIVO: Grade 3 (n=5) and Grade 2 (n=1). In Checkmate 069, immune-mediated hepatitis occurred in 15% (14/94) of patients receiving OPDIVO in combination with YERVOY: Grade 4 (n=3), Grade 3 (n=9), and Grade 2 (n=2).

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

Immune-Mediated Dermatitis

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 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

Hypophysitis, adrenal insufficiency, thyroid disorders, and type I diabetes mellitus can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer 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. Administer insulin for type I diabetes. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In Checkmate 025, hypophysitis occurred in 0.5% (2/406) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 1 (n=1). In Checkmate 069, hypophysitis occurred in 13% (12/94) of patients receiving OPDIVO in combination with YERVOY: Grade 3 (n=2) and Grade 2 (n=10). In Checkmate 037 and 057 (n=555), adrenal insufficiency occurred in 1% of patients receiving OPDIVO. In Checkmate 025, adrenal insufficiency occurred in 2% (8/406) of patients receiving OPDIVO: Grade 3 (n=3), Grade 2 (n=4), and Grade 1 (n=1). In Checkmate 069, adrenal insufficiency occurred in 9% (8/94) of patients receiving OPDIVO in combination with YERVOY: Grade 3 (n=3), Grade 2 (n=4), and Grade 1 (n=1). In Checkmate 037, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. In Checkmate 057, Grade 1 or 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) and elevated TSH occurred in 17% of patients receiving OPDIVO. Grade 1 or 2 hyperthyroidism occurred in 1.4% (4/287) of patients. In Checkmate 025, thyroid disease occurred in 43/406 (10.6%) patients receiving OPDIVO, including one Grade 3 event, and in 12/397 (3.0%) patients receiving everolimus. Hypothyroidism/thyroiditis occurred in 8.1% (33/406) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=17), and Grade 1 (n=14). Hyperthyroidism occurred in 2.5% (10/406) of patients receiving OPDIVO: Grade 2 (n=5) and Grade 1 (n=5). In Checkmate 069, hypothyroidism occurred in 19% (18/94) of patients receiving OPDIVO in combination with YERVOY. All were Grade 1 or 2 in severity except for one patient who experienced Grade 3 autoimmune thyroiditis. Grade 1 hyperthyroidism occurred in 2.1% (2/94) of patients receiving OPDIVO in combination with YERVOY. In Checkmate 025, hyperglycemic adverse events occurred in 37/406 (9%) patients. Diabetes mellitus or diabetic ketoacidosis occurred in 1% (6/406) of patients receiving OPDIVO: Grade 3 (n=3), Grade 2 (n=2), and Grade 1 (n=1).

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

Immune-mediated nephritis can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 increased serum creatinine, withhold and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue. In Checkmate 037, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients. In Checkmate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients receiving OPDIVO. In Checkmate 025, renal injury occurred in 6.6% (27/406) of patients receiving OPDIVO and 3.0% (12/397) of patients receiving everolimus. Immune-mediated nephritis and renal dysfunction occurred in 3.2% (13/406) of patients receiving OPDIVO: Grade 5 (n=1), Grade 4 (n=1), Grade 3 (n=5), and Grade 2 (n=6). In Checkmate 069, Grade 2 or higher immune-mediated nephritis or renal dysfunction occurred in 2.1% (2/94) of patients. One patient died without resolution of renal dysfunction.

Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4. In Checkmate 037 (n=268), the incidence of rash was 21%; the incidence of Grade 3 or 4 rash was 0.4%. In Checkmate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO including four Grade 3 cases. In Checkmate 025, rash occurred in 28% (112/406) of patients receiving OPDIVO and 36% (143/397) of patients receiving everolimus. Immune-mediated rash, defined as a rash treated with systemic or topical corticosteroids, occurred in 7.4% (30/406) of patients receiving OPDIVO: Grade 3 (n=4), Grade 2 (n=7), and Grade 1 (n=19). In Checkmate 069, immune-mediated rash occurred in 37% (35/94) of patients receiving OPDIVO in combination with YERVOY: Grade 3 (n=6), Grade 2 (n=10), and Grade 1 (n=19).

Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with OPDIVO treatment. 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. Across clinical trials of 8490 patients receiving OPDIVO as a single agent or in combination with YERVOY, <1% of patients were identified as having encephalitis. In Checkmate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO.

Other Immune-Mediated Adverse Reactions

Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy.

The following clinically significant immune-mediated adverse reactions occurred in <2% of single-agent OPDIVO-treated patients: uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, and systemic inflammatory response syndrome. Across clinical trials of OPDIVO administered as a single agent at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: facial nerve paralysis, motor dysfunction, vasculitis, and myasthenic syndrome. In Checkmate 069, the following additional immune-mediated adverse reactions occurred in 1% of patients treated with OPDIVO in combination with YERVOY: Guillain-Barré syndrome and hypopituitarism. Across clinical trials of OPDIVO in combination with YERVOY, the following additional clinically significant, immune-mediated adverse reactions were identified: uveitis, sarcoidosis, duodenitis, pancreatitis, and gastritis.

Infusion Reactions

Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO as a single agent. 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 Checkmate 057, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. In Checkmate 025, hypersensitivity/infusion-related reactions occurred in 6.2% (25/406) of patients receiving OPDIVO and 1.0% (4/397) of patients receiving everolimus. In Checkmate 069, Grade 2 infusion reactions occurred in 3% (3/94) of patients receiving OPDIVO in combination with YERVOY. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

Embryofetal 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 OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue nursing 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. 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 057, serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in $\geq 2\%$ of patients were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 069, serious adverse reactions occurred in 62% of patients receiving OPDIVO; the most frequent serious adverse events with OPDIVO in combination with YERVOY, as compared to YERVOY alone, were colitis (17% vs 9%), diarrhea (9% vs 7%), pyrexia (6% vs 7%), and pneumonitis (5% vs 0).

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction ($\geq 20\%$) reported with OPDIVO was rash (21%). In Checkmate 057, the most common adverse reactions ($\geq 20\%$) reported with OPDIVO were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%), and constipation (23%). In Checkmate 025, the most common adverse reactions ($\geq 20\%$) reported in patients receiving OPDIVO vs everolimus were asthenic conditions (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 069, the most common adverse reactions ($\geq 20\%$) reported in patients receiving OPDIVO in combination with YERVOY vs YERVOY alone were rash (67% vs 57%), pruritus (37% vs 26%), headache (24% vs 20%), vomiting (23% vs 15%), and colitis (22% vs 11%).

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

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

About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration

In 2011, through a collaboration 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, Bristol-Myers Squibb and Ono Pharmaceutical 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 www.bms.com, or follow us on Twitter at <http://twitter.com/bmsnews>.

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, 2014 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.

###

Media Inquiries:

Jaisy Wagner Styles
Office: 609-897-3958
Cell: 610-291-5168
jaisy.styles@bms.com

Investors:

Ranya Dajani
Office: 609-252-5330
ranya.dajani@bms.com

Bill Szablewski
Office: 609-252-5894
william.szablewski@bms.com

References

1. Opdivo Prescribing Information. Opdivo U.S. Product Information. Last updated: November 23, 2015. Princeton, NJ: Bristol-Myers
2. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.

3. American Cancer Society. Kidney cancer (adult) - renal cell carcinoma. www.cancer.org/acs/groups/cid/documents/webcontent/003107-pdf.pdf. Updated March 3, 2015. Accessed October 26, 2015.