

December 2, 2015

## **Bristol-Myers Squibb Announces Regulatory Update for Opdivo (nivolumab) in Advanced Melanoma**

(PRINCETON, NJ, November 27, 2015) – Bristol-Myers Squibb Company (NYSE:BMJ) announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter for its supplemental Biologics License Application (sBLA) for Opdivo (nivolumab) as a single agent for the treatment of previously untreated patients, specifically those with BRAF V600 mutation positive unresectable or metastatic melanoma. As part of the Complete Response Letter, the FDA indicated the need for additional data in the BRAF mutated patient population. Bristol-Myers Squibb is working to evaluate the request outlined by the FDA and will continue to work closely with the agency to determine whether additional data currently under review adequately addresses these comments.

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. 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. Also, Opdivo received expanded FDA approval in previously-treated metastatic non-small cell lung cancer in the same month. Furthermore, Opdivo was approved for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy, and for the treatment of patients with BRAF V600 wild-type (WT) unresectable or metastatic melanoma as a single agent in November 2015. 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: 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, etc. 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, Glioblastoma, Ovarian Cancer, etc.

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](mailto:public_relations@ono.co.jp)



## **Bristol-Myers Squibb Announces Regulatory Update for *Opdivo* (nivolumab) in Advanced Melanoma**

(PRINCETON, NJ, November 27, 2015) – [Bristol-Myers Squibb Company](#) (NYSE:BMJ) today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter for its supplemental Biologics License Application (sBLA) for *Opdivo* (nivolumab) as a single agent for the treatment of previously untreated patients, specifically those with *BRAF* V600 mutation positive unresectable or metastatic melanoma.

As part of the Complete Response Letter, the FDA indicated the need for additional data in the *BRAF* mutated patient population. Bristol-Myers Squibb is working to evaluate the request outlined by the FDA and will continue to work closely with the agency to determine whether additional data currently under review adequately addresses these comments.

The sBLA submitted for *Opdivo* as a single agent for previously untreated metastatic melanoma was based on clinical data from the Phase 3 CheckMate -066 trial which evaluated *Opdivo* in treatment-naïve patients with *BRAF* wild-type advanced melanoma compared to dacarbazine. The FDA approved *Opdivo* as a single agent for the treatment of patients with *BRAF* wild-type unresectable or metastatic melanoma, based on CheckMate -066, on November 23, 2015. In addition to data from CheckMate -066, the Company submitted data for *Opdivo* in *BRAF* V600 mutation positive metastatic melanoma, which was the subject of the FDA's Complete Response Letter.

A separate sBLA, which included data from CheckMate -067 evaluating *Opdivo* as a single agent and in combination with *Yervoy* (ipilimumab) in patients with previously untreated advanced melanoma, was accepted by the FDA for review in September and granted Priority Review with a target action date of January 23, 2016. Data for *Opdivo* monotherapy in both *BRAF* wild-type and *BRAF* V600 mutation positive advanced melanoma was included as part of this application.

### **Immuno-Oncology at Bristol-Myers Squibb**

Surgery, radiation, cytotoxic or targeted therapies have represented the mainstay of cancer treatment over the last several decades, but long-term survival and a positive quality of life have remained elusive for many patients with advanced disease.

To address this unmet medical need, Bristol-Myers Squibb is leading research in an innovative 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. The company is

exploring a variety of compounds and immunotherapeutic approaches for patients with different types of cancer, including researching the potential of combining Immuno-Oncology agents that target different pathways in the treatment of cancer.

Bristol-Myers Squibb is committed to advancing the science of Immuno-Oncology, with the goal of changing survival expectations and the way patients live with cancer.

## **INDICATIONS and IMPORTANT SAFETY INFORMATION for OPDIVO (nivolumab)**

### **INDICATIONS**

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

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with unresectable or metastatic, BRAF V600 mutation-positive melanoma and disease progression following ipilimumab and 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 the confirmatory trials.

OPDIVO® (nivolumab), 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 the 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.

### **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 addition, in Checkmate 069, there were six 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 066, immune-mediated pneumonitis occurred in 1.4% (3/206) of patients receiving OPDIVO and in none of the 205 patients receiving dacarbazine: Grade 2 (n=3). 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% (21/406) of patients receiving OPDIVO and 18% (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 066, diarrhea or colitis occurred in 28% (58/206) of patients receiving OPDIVO and 25% (52/205) of patients receiving dacarbazine. Immune-mediated colitis occurred in 4.9% (10/206) of patients receiving OPDIVO: Grade 3 (n=5) and Grade 2 (n=5). 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  $\geq 7$  stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that study (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

### **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 066, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the dacarbazine-treated group, with increases in ALT (25% vs. 19%), AST (24% vs. 19%), alkaline phosphatase (21% vs. 14%), and total bilirubin (13% vs. 6%). Immune-mediated hepatitis occurred in 0.9% (2/206) of patients receiving OPDIVO: Grade 3 (n=1) 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 3.5%) 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 1 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 1 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, 066, 057, <1.0% of OPDIVO-treated patients developed adrenal insufficiency. In Checkmate 025, adrenal insufficiency occurred in 2.0% (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 3.0% (8/268) of patients receiving OPDIVO and 1.0% (1/102) of patients receiving chemotherapy. In Checkmate 066, hypothyroidism occurred in 7% (14/206) of patients receiving OPDIVO (Grade 3 (n=1)) and 0.9% (2/205) of patients receiving dacarbazine. Hyperthyroidism occurred in 4.4% (9/206) of patients receiving OPDIVO (Grade 3 (n=1)) and 0.9% (2/205) of patients receiving dacarbazine. 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 11% (43/406) of patients receiving OPDIVO, including one Grade 3 event, and in 3.0% (12/397) of patients receiving everolimus. Hypothyroidism/thyroiditis occurred in 8% (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 066, diabetes mellitus or diabetic ketoacidosis occurred in 1.0% (2/206) of patients receiving OPDIVO and none of the 205 receiving dacarbazine; Grade 3 diabetic ketoacidosis (n=1) and Grade 2 diabetes mellitus (n=1). In Checkmate 025, hyperglycemic adverse events occurred in 9% (37/406) patients. Diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (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 066, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the dacarbazine-treated group (11% vs. 10%). Grade 3 immune-mediated renal dysfunction occurred in 0.5% (1/206) 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 7% (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 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% (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, <1.0% 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 <1.0% of OPDIVO-treated patients: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barre syndrome, hypopituitarism 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: motor dysfunction, vasculitis, and myasthenic syndrome. Across clinical trials of OPDIVO in combination with YERVOY, the following additional clinically significant, immune-mediated adverse reactions were identified: sarcoidosis, duodenitis, and gastritis.

## **Infusion Reactions**

Severe infusion reactions have been reported in <1.0% 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 and 066, Grade 2 infusion reactions occurred in 1.0% (5/493) of patients receiving OPDIVO. In Checkmate 025, hypersensitivity/infusion-related reactions occurred in 6% (25/406) of patients receiving OPDIVO and 1.0% (4/397) of patients receiving everolimus. In Checkmate 069, Grade 2 infusion reactions occurred in 3.2% (3/94) of patients receiving OPDIVO in combination with YERVOY.

## **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 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions

reported in  $\geq 2\%$  of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). 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  $\geq 2\%$  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 066, the most common adverse reactions ( $\geq 20\%$ ) reported with OPDIVO vs dacarbazine were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). 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, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY.](#)

[Please see U.S. Full Prescribing Information for OPDIVO.](#)

### **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, 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](http://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](mailto:jaisy.styles@bms.com)

#### **Investors:**

Ranya Dajani  
Office: 609-252-5330  
[ranya.dajani@bms.com](mailto:ranya.dajani@bms.com)

Bill Szablewski  
Office: 609-252-5894  
[william.szablewski@bms.com](mailto:william.szablewski@bms.com)