November 30, 2015

Bristol-Myers Squibb Announces U.S. Food and Drug Administration Approval for Opdivo (nivolumab) as a Single Agent for the Treatment of Patients with Previously Untreated BRAF Wild-Type Advanced Melanoma

(PRINCETON, NJ, November 24, 2015) – Bristol-Myers Squibb Company (NYSE:BMY) announced that the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) injection, for intravenous use, as a single agent for the treatment of patients with BRAF V600 wild-type (WT) unresectable or metastatic melanoma. The approval is based on data from the Phase 3 trial, CheckMate -066, which evaluated overall survival as the primary endpoint in treatment-naïve patients with BRAF WT unresectable or metastatic melanoma compared to chemotherapy (dacarbazine).

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 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

Bristol-Myers Squibb Announces U.S. Food and Drug Administration Approval for *Opdivo* (nivolumab) as a Single Agent for the Treatment of Patients with Previously Untreated *BRAF* Wild-Type Advanced Melanoma

First and only PD-1 immune checkpoint inhibitor approved as a single agent for first-line use in advanced BRAF wild-type melanoma

Approval based on Phase 3 trial, CheckMate -066, which demonstrated superior overall survival vs. dacarbazine in first-line treatment of patients with BRAF wild-type advanced melanoma

Marks the sixth FDA approval for Opdivo *in the past 12 months*

(PRINCETON, NJ, November 24, 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, as a single agent for the treatment of patients with *BRAF* V600 wild-type (WT) unresectable or metastatic melanoma. The approval is based on data from the Phase 3 trial, CheckMate -066, which evaluated overall survival as the primary endpoint in treatment-naïve patients with *BRAF* WT unresectable or metastatic melanoma compared to chemotherapy (dacarbazine).

"Our focused approach to Immuno-Oncology research is to deliver treatment options that have the potential to improve long-term survival outcomes for patients," said Michael Giordano, M.D., senior vice president, head of Oncology Development, Bristol-Myers Squibb. "*Opdivo* has become a critical part of the treatment landscape for advanced melanoma patients and their physicians, both as a monotherapy and in combination, and we are committed to exploring opportunities for this treatment across stages of disease and lines of therapy."

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 additional Important Safety Information section below.

"Advanced melanoma continues to be one of the deadliest and most challenging cancers to treat, and ongoing research in Immuno-Oncology from clinical trials like CheckMate -066 shows the potential to provide improved overall survival for newly diagnosed patients with *BRAF* wild-type metastatic melanoma," said Jeffrey S. Weber, M.D., PhD, deputy director of the Laura and Isaac Perlmutter Cancer Center at the NYU Langone Medical Center. "This important news means that we now have another new option to offer patients with *BRAF* wild-type metastatic melanoma."

A supplemental Biologics License Application for *Opdivo* in *BRAF* V600 mutation positive unresectable or metastatic melanoma, which was filed subsequent to data from CheckMate -066, is still under review with the FDA.

<u>*Opdivo* Demonstrated Efficacy in Newly Diagnosed *BRAF* Wild-Type Advanced Melanoma</u>

CheckMate -066 is a Phase 3, randomized, double-blind study of treatment-naïve patients with unresectable or metastatic *BRAF* WT melanoma. Patients were randomized to receive *Opdivo* (intravenously 3 mg/kg q2w; n=210) or dacarbazine (intravenously 1000 mg/m2 q3w; n=208). The primary efficacy endpoint of the trial was overall survival (OS), and secondary endpoints were progression-free survival (PFS) and objective response rate (ORR).

In the trial, *Opdivo* demonstrated superior OS versus chemotherapy in the first-line setting. Results were based on the interim analysis conducted on 47% of the total planned events for OS (50 for the *Opdivo* arm; 96 for the dacarbazine arm). The median OS was not reached for *Opdivo* and was 10.8 months (95% CI: 9.3-12.1) in the dacarbazine arm (HR=0.42; 95% CI: 0.30-0.60; p<0.0001). Median PFS more than doubled with *Opdivo* (5.1 months [95% CI: 3.5-10.8] vs. 2.2 months [95% CI: 2.1-2.4] for patients treated with dacarbazine [HR=0.43; 95% CI: 0.34-0.56; p<0.0001]). ORR with *Opdivo* was 34% (4% complete response rate, 30% partial response rate [95% CI: 28-41]) compared to 9% with dacarbazine (1% complete response rate, 8% partial response rate [95% CI: 5-13]). At the time of analysis, 88% (63/72) of *Opdivo*-treated patients had ongoing responses, which included 43 patients with ongoing responses of six months or longer.

Last year, the CheckMate -066 trial was stopped early following a recommendation by the independent Data Monitoring Committee based on their analysis which showed evidence of superior OS in patients receiving *Opdivo* compared to the control arm. As a result, patients in the trial were unblinded and patients who had received dacarbazine were allowed to receive *Opdivo*. Dacarbazine was selected as the comparator in this study because, at the time the study protocol was designed, it represented the standard of care in many regions outside of the U.S where *Yervoy* had not yet been approved for first-line use.

In the trial, 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 ≥2% of patients receiving *Opdivo* were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). Adverse reactions led to permanent discontinuation of *Opdivo* in 7% of patients and dose interruption in 26% of patients. The most common adverse reactions in

CheckMate -066 (≥20%) reported with *Opdivo* versus dacarbazine were fatigue (49% vs. 39%), musculoskeletal pain (32% vs. 25%), rash (28% vs. 12%), and pruritus (23% vs. 12%).

About Advanced Melanoma

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin. Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to the other organs, such as the lymph nodes, lungs, brain or other areas of the body. The incidence of melanoma has been increasing for at least 30 years. In the U.S., more than 73,000 cases of melanoma will be diagnosed this year and nearly 10,000 people are expected to die from the disease. Melanoma is mostly curable when treated in its early stages. However, in its late stages, the average survival rate has historically been just six months with a one-year survival rate of 25.5%, making it one of the most aggressive forms of cancer.

Leading Immuno-Oncology Development in Melanoma

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.

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 for *Opdivo*

Bristol-Myers Squibb remains committed to helping patients through treatment with *Opdivo*. 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 *Opdivo* specific reimbursement information, please visit the BMS Access Support Product section by visiting www.bmsaccesssupportopdivo.com.

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.

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

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 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 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 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 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 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% of OPDIVO-treated patients developed adrenal insufficiency. 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 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 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 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 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. 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 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, systemic inflammatory response syndrome, Guillain-Barre syndrome and hypopituitarism. 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 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 ≥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 ≥2% of patients were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. 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 (≥20%) reported with OPDIVO was rash (21%). In Checkmate 066, the most common adverse reactions (≥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 (≥20%) reported with OPDIVO were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%), and constipation (23%). In Checkmate 069, the most common adverse reactions (≥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 (≥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.

Indication

YERVOY® (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS YERVOY (ipilimumab) 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.

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

Recommended Dose Modifications
Endocrine: Withhold YERVOY for systemic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

Immune-mediated Enterocolitis
Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms. Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent). Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence

or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3-5 days or recurring after symptom improvement. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis. Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

Immune-mediated Hepatitis

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY. Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution. Withhold YERVOY in patients with Grade 2 hepatotoxicity. Permanently discontinue YERVOY in patients with Grade 3-4 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5× the ULN or total bilirubin elevations >3× the ULN; Grade 3-5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4%. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5× but ≤5× the ULN or total bilirubin elevation >1.5× but ≤3× the ULN; Grade 2). In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID).

Immune-mediated Dermatitis

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically; administer topical or systemic corticosteroids if there is no improvement within 1 week. Withhold YERVOY in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., 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 YERVOY-treated patients (2.5%); 1 patient (0.2%) died as a result of toxic epidermal necrolysis and 1 additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis.

Immune-mediated Neuropathies

Immune-mediated neuropathies, including fatal cases, can occur with YERVOY. Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities). Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities), such as Guillain-Barre-like syndromes. Institute medical intervention as appropriate for management for severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. In patients receiving YERVOY 3 mg/kg in Trial 1, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Immune-mediated Endocrinopathies

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY. Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may

resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediated. Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Withhold YERVOY in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. In patients receiving YERVOY 3 mg/kg in Trial 1, 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 YERVOY-treated patients (1.8%). All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY.

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. In Trial 1, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia. Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with <1% incidence: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, hemolytic anemia, and nephritis.

Embryo-fetal Toxicity

Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY.

Lactation

It is not known whether YERVOY is secreted in human milk. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

Common Adverse Reactions

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

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

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, 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