

May 20, 2016

**European Commission Approves the First and Only Immuno-Oncology Combination,
Opdivo® (nivolumab) + Yervoy® (ipilimumab) Regimen,
for Treatment of Advanced Melanoma**

(PRINCETON, NJ, May 11, 2016) – Bristol-Myers Squibb Company (NYSE: BMY) announced that the European Commission (EC) has approved Opdivo in combination with Yervoy for the treatment of advanced (unresectable or metastatic) melanoma in adults, representing the first and only approved combination of two Immuno-Oncology agents in the European Union (EU). This approval allows for the marketing of the Opdivo + Yervoy Regimen in all 28 Member States of the EU. Approval was based on CheckMate -067, the first Phase 3, double-blind, randomized study, in which the Opdivo + Yervoy Regimen and Opdivo monotherapy demonstrated superior progression-free survival (PFS) and objective response rates (ORR) in patients with advanced melanoma, regardless of BRAF mutational status, versus Yervoy alone.

Bristol-Myers Squibb (BMS) has a robust clinical development program in Opdivo monotherapy and in combination therapy with other therapeutic drugs in a variety of tumor types overseas, including Head and Neck Cancer, Glioblastoma, Small Cell Lung Cancer, Urothelial Cancer, Hepatocellular Carcinoma, Esophageal Cancer, Hodgkin Lymphoma, Colorectal Cancer, Solid Tumors (Triple-Negative Breast Cancer, Gastric Cancer, Pancreatic Cancer), Blood Cancer, etc.

In Japan, Ono Pharmaceutical Co., Ltd. (ONO) launched Opdivo for the treatment of unresectable melanoma in September 2014. ONO received an approval for additional indication of unresectable, advanced or recurrent non-small cell lung cancer in December 2015. In addition, ONO has submitted supplemental applications for additional indications of Renal Cell Cancer and Hodgkin Lymphoma, and is conducting clinical development program including Head and Neck Cancer, Gastric Cancer, Esophageal Cancer, Small Cell Lung Cancer, Hepatocellular Carcinoma, Glioblastoma, Ovarian Cancer, Urothelial Cancer, Biliary Tract Cancer, etc.

In Japan, ONO and BMS (and BMS Japan subsidiary BMSKK) have formed a strategic partnership that includes co-development, co-commercialization, and co-promotion of multiple immunotherapies for patients with cancer.

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



European Commission Approves the First and Only Immuno-Oncology Combination, Bristol-Myers Squibb's *Opdivo*® (nivolumab) + *Yervoy*® (ipilimumab) Regimen, for Treatment of Advanced Melanoma

Opdivo + Yervoy Regimen now approved for unresectable or metastatic melanoma patients, regardless of BRAF mutational status

Approval of the Regimen marks a novel combination treatment for advanced melanoma patients, demonstrating the potential of targeting distinct and complementary immune pathways

With this fifth EU approval for Opdivo, in three distinct tumor types, more patients fighting cancer have access to Immuno-Oncology treatment options in Europe

(PRINCETON, NJ, May 11, 2016) – [Bristol-Myers Squibb Company](#) (NYSE: BMY) announced today that the European Commission (EC) has approved *Opdivo* in combination with *Yervoy* for the treatment of advanced (unresectable or metastatic) melanoma in adults, representing the first and only approved combination of two Immuno-Oncology agents in the European Union (EU). This approval allows for the marketing of the *Opdivo + Yervoy* Regimen in all 28 Member States of the EU. Approval was based on CheckMate -067, the first Phase 3, double-blind, randomized study, in which the *Opdivo + Yervoy* Regimen and *Opdivo* monotherapy demonstrated superior progression-free survival (PFS) and objective response rates (ORR) in patients with advanced melanoma, regardless of *BRAF* mutational status, versus *Yervoy* alone. The safety profile was consistent with previously reported studies evaluating the *Opdivo + Yervoy* Regimen, and most treatment-related adverse events were managed using established algorithms.

Dr. James Larkin, from The Royal Marsden and lead author on CheckMate -067, the trial that led to this approval, commented, “Historically, advanced melanoma has been a very difficult-to-treat disease. Now, with this approval, patients in Europe will have a treatment option combining two Immuno-Oncology therapies, *Opdivo* and *Yervoy*, which in a Phase 3 randomized trial has shown its ability to deliver superior efficacy versus *Yervoy* monotherapy in progression-free survival and response. This is truly good news for healthcare providers and the patients they treat, as it represents an important new treatment option with the potential for improved outcomes.”

In study CheckMate -067, the *Opdivo + Yervoy* Regimen demonstrated a 58% reduction in the risk of disease progression versus *Yervoy* monotherapy in previously untreated patients with advanced melanoma (HR=0.42 [99.5% CI: 0.32-0.56; $p<0.0001$]), while *Opdivo* monotherapy demonstrated a

45% risk reduction versus *Yervoy* monotherapy (HR=0.55 [99.5% CI: 0.42-0.73; $p<0.0001$]). The median PFS for the *Opdivo* + *Yervoy* Regimen was 11.5 months (95% CI: 8.9-22.18) and 6.9 months (95% CI: 4.3-9.5) for *Opdivo* monotherapy versus 2.89 months (95% CI: 2.8-3.4) for *Yervoy* monotherapy, at a minimum follow-up of 18 months. The *Opdivo* + *Yervoy* Regimen and *Opdivo* monotherapy also demonstrated a higher ORR (ORR: 58% and 44%, $p<0.0001$, respectively) versus *Yervoy* monotherapy (19%). Median duration of response was not reached for the *Opdivo* + *Yervoy* Regimen and was 22.3 months for *Opdivo* monotherapy, versus 14.4 months for *Yervoy* alone.

Based on a pre-planned, descriptive analysis of data from CheckMate -067, the EC adopted the Committee for Medicinal Products for Human Use (CHMP) recommendation to add an informative statement to the broad indication that relative to *Opdivo* monotherapy, an increase in PFS for the combination of *Opdivo* with *Yervoy* is established only in patients with low tumor PD-L1 expression. In the study, overall response rates were higher for the combination of *Opdivo* and *Yervoy* relative to *Opdivo* monotherapy across tumor PD-L1 expression levels.

The approval was also based on supportive data from the Phase 2 study, CheckMate -069, in which the *Opdivo* + *Yervoy* Regimen demonstrated an ORR, the primary endpoint, of 61% (95% CI: 48.9-72.4) in patients with *BRAF* wild-type advanced melanoma, versus 11% (95% CI: 3-25.4) ORR in the *Yervoy* monotherapy arm, with a minimum follow-up of 11 months. The estimated 12- and 18-month overall survival (OS) rates were 79% (95% CI: 67, 87) and 73% (95% CI: 61, 82), respectively, for the *Opdivo* + *Yervoy* Regimen, and 62% (95% CI: 44, 75) and 56% (95% CI: 39, 70), respectively, for *Yervoy* monotherapy. The OS data are based on an exploratory, pre-planned analysis of patients with *BRAF* wild-type advanced melanoma.

Emmanuel Blin, senior vice president, Head of Commercialization, Policy and Operations, Bristol-Myers Squibb, commented, “Today’s approval of the *Opdivo* + *Yervoy* Regimen for advanced melanoma patients supports our goal of developing innovative treatment approaches that have the potential to improve patient outcomes. The *Opdivo* + *Yervoy* Regimen is the first and only approved Immuno-Oncology combination, and only Regimen to deliver superior efficacy compared to *Yervoy*, and we are thrilled to make this novel combination treatment available to patients with advanced melanoma in Europe.”

Approval Based on Superior Efficacy Demonstrated Versus *Yervoy* In Pivotal Phase 3 Study

CheckMate -067 is a Phase 3, double-blind, randomized study that evaluated the *Opdivo* + *Yervoy* Regimen or *Opdivo* monotherapy versus *Yervoy* alone in patients with previously untreated

advanced melanoma, including both *BRAF* V600 mutation positive or *BRAF* wild-type advanced melanoma. A total of 945 patients were randomized to receive the *Opdivo* + *Yervoy* Regimen (*Opdivo* 1 mg/kg plus *Yervoy* 3 mg/kg every 3 weeks for 4 doses followed by *Opdivo* 3 mg/kg every 2 weeks thereafter; n=314), *Opdivo* monotherapy (*Opdivo* 3 mg/kg every 2 weeks; n=316) or *Yervoy* monotherapy (*Yervoy* 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks; n=315). Randomization was stratified by PD-L1 expression ($\geq 5\%$ vs. $< 5\%$), *BRAF* status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Patients were treated until progression or unacceptable toxicity. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS); the study is ongoing and patients continue to be followed for OS. Objective response rate (ORR) and the duration of response were also assessed.

Results from the trial demonstrated a statistically significant improvement in PFS in patients with advanced melanoma treated with the *Opdivo* + *Yervoy* Regimen ($p < 0.0001$) and with *Opdivo* as a single agent ($p < 0.0001$) versus *Yervoy* monotherapy. At a minimum follow-up of 18 months, the *Opdivo* + *Yervoy* Regimen demonstrated a 58% reduction in the risk of disease progression versus *Yervoy* monotherapy in previously untreated patients with advanced melanoma (HR=0.42 [99.5% CI: 0.32-0.56; $p < 0.0001$]), while *Opdivo* monotherapy demonstrated a 45% risk reduction versus *Yervoy* monotherapy (HR=0.55 [99.5% CI: 0.42-0.73; $p < 0.0001$]). The median PFS for the *Opdivo* + *Yervoy* Regimen was 11.5 months (95% CI: 8.9-22.18) and 6.9 months (95% CI: 4.3-9.5) for *Opdivo* monotherapy versus 2.89 months (95% CI: 2.8-3.4) for *Yervoy* monotherapy, at a minimum follow-up of 18 months.

The *Opdivo* + *Yervoy* Regimen and *Opdivo* monotherapy also demonstrated a higher ORR (ORR: 58% and 44%, $p < 0.0001$, respectively) versus *Yervoy* monotherapy (19%). There were 38 (12%) complete responses and 143 (46%) partial responses seen in patients treated with the *Opdivo* + *Yervoy* Regimen, and 31 (10%) complete responses and 107 (34%) partial responses seen in patients treated with *Opdivo* monotherapy, versus 7 (2%) complete responses and 53 (17%) partial responses seen in patients treated with *Yervoy* alone. Median duration of response was not reached (0+ - 24+ months) for the *Opdivo* + *Yervoy* Regimen and was 22.3 months (0+ - 23+) for *Opdivo* monotherapy, versus 14.4 months (1.4 - 22.3+) for *Yervoy* alone.

CheckMate -069 is a Phase 2, double-blind, randomized study evaluating the *Opdivo* + *Yervoy* Regimen versus *Yervoy* monotherapy in 142 patients with previously untreated unresectable or metastatic melanoma. The trial included patients with *BRAF* V600 mutation positive and *BRAF* wild-type advanced melanoma, and randomization was stratified by *BRAF* mutation status. The primary

endpoint was ORR in patients with *BRAF* wild-type tumors. Secondary endpoints included PFS in patients with *BRAF* wild-type tumors, ORR in patients with *BRAF* V600 mutation positive tumors and safety. Overall survival was an exploratory endpoint. Treatment was continued until progression or unacceptable toxicity. In this study, the *Opdivo* + *Yervoy* Regimen demonstrated a response rate of 61% (95% CI: 48.9-72.4) in patients with *BRAF* wild-type advanced melanoma, versus 11% (95% CI: 3-25.4) ORR in the *Yervoy* monotherapy arm, with a minimum follow-up of 11 months. The estimated 12- and 18-month OS rates were 79% (95% CI: 67, 87) and 73% (95% CI: 61, 82), respectively, for the *Opdivo* + *Yervoy* Regimen, and 62% (95% CI: 44, 75) and 56% (95% CI: 39, 70), respectively, for *Yervoy*.

In a pooled dataset of the *Opdivo* + *Yervoy* Regimen, based on three studies of the combination, the most frequent adverse reactions ($\geq 10\%$) were rash (51%), fatigue (43%), diarrhea (42%), pruritus (35%), nausea (25%), pyrexia (19%), decreased appetite (15%), hypothyroidism (15%), vomiting (14%), colitis (14%), abdominal pain (13%), arthralgia (11%) and headache (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Among the patients treated with *Opdivo* in combination with *Yervoy* in CheckMate -067, 151/313 (48%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 37 (25%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

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. Melanoma is the ninth most common cancer in Europe, with an estimated 100,000 new cases diagnosed annually and more than 20,000 deaths.

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

At Bristol-Myers Squibb, we have a vision for the future of cancer care that is focused on Immuno-Oncology, now considered a major treatment modality alongside surgery, radiation and chemotherapy for certain types of cancer.

We have a comprehensive clinical portfolio of investigational and approved Immuno-Oncology agents, many of which were discovered and developed by our scientists. We pioneered the research leading to the first regulatory approval for the combination of two Immuno-Oncology agents, and continue to study the role of combinations in cancer.

Our collaboration with academia, as well as small and large biotech companies is responsible for researching the potential of Immuno-Oncology and non-Immuno-Oncology combinations, with the goal of providing new treatment options in clinical practice.

At Bristol-Myers Squibb, we are committed to changing expectations in hard-to-treat cancers and the way patients live with cancer.

About Opdivo

Cancer cells may exploit “regulatory” pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack. *Opdivo* is a PD-1 immune checkpoint inhibitor that binds to the checkpoint receptor PD-1 expressed on activated T-cells, and blocks the binding of PD-L1 and PD-L2, preventing the PD-1 pathway’s suppressive signaling on the immune system, including the interference with an anti-tumor immune response.

Opdivo’s broad global development program is based on Bristol-Myers Squibb’s understanding of the biology behind Immuno-Oncology. Our company is at the forefront of researching the potential of Immuno-Oncology to extend survival in hard-to-treat cancers. This scientific expertise serves as the basis for the *Opdivo* development program, which includes a broad range of Phase 3 clinical trials evaluating overall survival as the primary endpoint across a variety of tumor types. The *Opdivo* trials have also contributed toward the clinical and scientific understanding of the role of biomarkers and how patients may benefit from *Opdivo* across the continuum of PD-L1 expression. To date, the *Opdivo* clinical development program has enrolled more than 18,000 patients.

Opdivo was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world in July 2014, and currently has regulatory approval in 50 countries including the United States, Japan, and in the European Union.

U.S. FDA APPROVED 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 BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma. This indication is approved under accelerated

approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in 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, 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 069 and 067, immune-mediated pneumonitis occurred in 6% (25/407) of patients receiving OPDIVO with YERVOY: Fatal (n=1), Grade 3 (n=6), Grade 2 (n=17), and Grade 1 (n=1). In Checkmate 037, 066, and 067, immune-mediated pneumonitis occurred in 1.8% (14/787) of patients receiving OPDIVO: Grade 3 (n=2) and Grade 2 (n=12). 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).

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. When administered with YERVOY, withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis upon restarting OPDIVO. In Checkmate 069 and 067, diarrhea or colitis occurred in 56% (228/407) of patients receiving OPDIVO with YERVOY. Immune-mediated colitis occurred in 26% (107/407) of patients: Grade 4 (n=2), Grade 3 (n=60), Grade 2 (n=32), and Grade 1 (n=13). In Checkmate 037, 066, and 067, diarrhea or colitis occurred in 31% (242/787) of patients receiving OPDIVO. Immune-mediated colitis occurred in 4.1% (32/787) of patients: Grade 3 (n=20), Grade 2 (n=10), and Grade 1 (n=2). 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 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 069 and 067, immune-mediated hepatitis occurred in 13% (51/407) of patients receiving OPDIVO with YERVOY: Grade 4 (n=8), Grade 3 (n=37), Grade 2 (n=5), and Grade 1 (n=1). In Checkmate 037, 066, and 067, immune-mediated hepatitis occurred in 2.3% (18/787) of patients receiving OPDIVO: Grade 4 (n=3), Grade 3 (n=11), and Grade 2 (n=4). 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 and everolimus arms, 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 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 069 and 067, hypophysitis occurred in 9% (36/407) of patients receiving OPDIVO with YERVOY: Grade 3 (n=8), Grade 2 (n=25), and Grade 1 (n=3). In Checkmate 037, 066, and 067, hypophysitis occurred in 0.9% (7/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=3), and Grade 1 (n=2). 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 and 067, adrenal insufficiency occurred in 5% (21/407) of patients receiving OPDIVO with YERVOY: Grade 4 (n=1), Grade 3 (n=7), Grade 2 (n=11), and Grade 1 (n=2). In Checkmate 037, 066, and 067, adrenal insufficiency occurred in 1% (8/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=5), and Grade 1 (n=1). In Checkmate 057, 0.3% (1/287) 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 and 067, hypothyroidism or thyroiditis occurred in 22% (89/407) of patients receiving OPDIVO with YERVOY: Grade 3 (n=6), Grade 2 (n=47), and Grade 1 (n=36). Hyperthyroidism occurred in 8% (34/407) of patients: Grade 3 (n=4), Grade 2 (n=17), and Grade 1 (n=13). In Checkmate 037, 066, and 067, hypothyroidism or thyroiditis occurred in 9% (73/787) of patients receiving OPDIVO: Grade 3 (n=1), Grade 2 (n=37), Grade 1 (n=35). Hyperthyroidism occurred in 4.4% (35/787) of patients receiving OPDIVO: Grade 3 (n=1), Grade 2 (n=12), and Grade 1 (n=22). In Checkmate 057, Grade 1 or 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) and elevated thyroid stimulating hormone 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 and 067, diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/407) of patients: Grade 4 (n=3), Grade 3 (n=1), Grade 2 (n=1), and Grade 1 (n=1). In Checkmate 037, 066, and 067, diabetes mellitus or diabetic ketoacidosis occurred in 0.8% (6/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=3), and Grade 1 (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 069 and 067, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients: Grade 4 (n=4), Grade 3 (n=3), and Grade 2 (n=2). In Checkmate 037, 066, and 067, nephritis and renal dysfunction of any grade occurred in 5% (40/787) of patients receiving OPDIVO. Immune-mediated nephritis and renal dysfunction occurred in 0.8% (6/787) of patients: Grade 3 (n=4) and Grade 2 (n=2). 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).

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 069 and 067, immune-mediated rash occurred in 22.6% (92/407) of patients receiving OPDIVO with YERVOY: Grade 3 (n=15), Grade 2 (n=31), and Grade 1 (n=46). In Checkmate 037, 066, and 067, immune-mediated rash occurred in 9% (72/787) of patients receiving OPDIVO: Grade 3 (n=7), Grade 2 (n=15), and Grade 1 (n=50). 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).

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. In Checkmate 067, encephalitis was identified in one patient (0.2%) receiving OPDIVO with YERVOY. 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. In < 1.0% of patients receiving OPDIVO, the following clinically significant, immune-mediated adverse reactions occurred: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, and sarcoidosis. Across clinical trials of OPDIVO as a single agent administered at doses of 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions

Severe infusion reactions have been reported in <1.0% of patients in clinical trials of OPDIVO. 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 069 and 067, infusion-related reactions occurred in 2.5% (10/407) of patients receiving OPDIVO with YERVOY: Grade 2 (n=6) and Grade 1 (n=4). In Checkmate 037, 066, and 067, Grade 2 infusion related reactions occurred in 2.7% (21/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=8), and Grade 1 (n=11). In Checkmate 057, Grade 2 infusion reactions requiring corticosteroids occurred in 1.0% (3/287) 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.

Embryo-fetal Toxicity

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

Lactation

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

Serious Adverse Reactions

In Checkmate 067, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) all occurred more frequently in the OPDIVO plus YERVOY arm relative to the OPDIVO arm. The most frequent ($\geq 10\%$) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). 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.

Common Adverse Reactions

In Checkmate 067, the most common ($\geq 20\%$) adverse reactions in the OPDIVO plus YERVOY arm were fatigue (59%), rash (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common ($\geq 20\%$) adverse reactions in the OPDIVO arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). 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 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%).

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

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Ltd (Ono) Bristol-Myers Squibb expanded its territorial rights to develop and commercialize Opdivo globally except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Bristol-Myers Squibb and Ono further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on [LinkedIn](#), [Twitter](#), [YouTube](#) and [Facebook](#).

Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2015 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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Contacts:

Media:

Audrey Abernathy, 609-419-5375, cell: 919-605-4521, audrey.abernathy@bms.com

Investors:

Ranya Dajani, 609-252-5330, ranya.dajani@bms.com or Bill Szablewski, 609-252-5894, william.szablewski@bms.com