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**Bristol-Myers Squibb's Opdivo (nivolumab) + Yervoy (ipilimumab) Regimen  
Receives Expanded FDA Approval  
in Unresectable or Metastatic Melanoma Across BRAF Status**

(PRINCETON, NJ, January 23, 2016) – Bristol-Myers Squibb Company (NYSE: BMY) announced that the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for the treatment of patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival (PFS). FDA also expands use of Opdivo as single-agent to include previously untreated BRAF mutation-positive advanced melanoma patients, based on accelerated approval

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. ONO was approved for the treatment of patients with unresectable, advanced or recurrent NSCLC in December 2015. 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.

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**Bristol-Myers Squibb's *Opdivo* (nivolumab) + *Yervoy* (ipilimumab) Regimen Receives Expanded FDA Approval in Unresectable or Metastatic Melanoma Across *BRAF* Status<sup>1</sup>**

- *Opdivo + Yervoy Regimen now indicated for unresectable or metastatic melanoma patients, regardless of BRAF mutational status, based on accelerated approval<sup>1</sup>*
- *Demonstrated significantly superior progression-free survival vs. Yervoy alone in CheckMate -067 with the first and only FDA-approved combination of immune checkpoint inhibitors<sup>1,2</sup>*
- *FDA also expands use of Opdivo as single-agent to include previously untreated BRAF mutation-positive advanced melanoma patients, based on accelerated approval<sup>1</sup>*
- *With this seventh approval for Opdivo in just over a year, and the fourth for late-stage melanoma, more patients fighting cancer now have access to Immuno-Oncology treatment options<sup>1</sup>*

(PRINCETON, NJ, January 23, 2016) – [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved *Opdivo* (nivolumab) in combination with *Yervoy* (ipilimumab) for the treatment of patients with *BRAF* V600 wild-type and *BRAF* V600 mutation-positive unresectable or metastatic melanoma.<sup>1</sup> This indication is approved under accelerated approval based on progression-free survival (PFS).<sup>1</sup> Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.<sup>1</sup> This approval expands the original indication for the *Opdivo + Yervoy* Regimen for the treatment of patients with *BRAF* V600 wild-type unresectable or metastatic melanoma to include patients, regardless of *BRAF* mutational status, based on data from the Phase 3 CheckMate -067 trial, in which PFS and overall survival (OS) were co-primary endpoints.<sup>1,2</sup>

*Opdivo* is associated with immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryofetal toxicity.<sup>1</sup> Please see the Important Safety Information section below, including Boxed WARNING for *Yervoy* regarding immune-mediated adverse reactions.

“For nearly a decade, our researchers have worked tirelessly to find treatment options that could improve outcomes for patients with late-stage melanoma, a particularly aggressive cancer, and we are incredibly proud of today’s approval to expand the use of the *Opdivo + Yervoy* Regimen to include patients with *BRAF* mutation-positive unresectable or metastatic melanoma. CheckMate -067 is the first Phase 3 study to observe the efficacy and safety of both *Opdivo* as a single-agent as well as in combination with *Yervoy* versus *Yervoy* alone,” said Chris Boerner, Head of U.S. Commercial, Bristol-Myers Squibb. “To make this treatment option available to more patients is truly a milestone in the fight against this deadly disease.”

The FDA also expanded the use of *Opdivo* as a single-agent to include previously untreated *BRAF* mutation-positive advanced melanoma patients.<sup>1</sup> The use of *Opdivo* as a single-agent in patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma is approved under accelerated approval based on progression-free survival.<sup>1</sup> Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.<sup>1</sup> *Opdivo* was approved by the FDA in November 2015, for use in previously untreated patients with *BRAF* V600 wild-type unresectable or metastatic melanoma.<sup>1</sup>

“Patients with metastatic melanoma historically have a very challenging disease. Recent advances in our understanding of the immune response to cancer has yielded therapies which provide meaningful responses and hope. The combination of two Immuno-Oncology treatments, nivolumab and ipilimumab, has been shown to provide these patients with a much needed improvement in progression-free survival and response rates,” said Jedd D. Wolchok, MD, PhD, Chief, Melanoma and Immunotherapeutics Service, Department of Medicine and Ludwig Center at Memorial Sloan Kettering Cancer Center. “This expanded approval for the nivolumab and ipilimumab regimen provides more advanced melanoma patients with an Immuno-Oncology combination treatment, and the potential for improved outcomes.”

### **Expanded Approval Based on Efficacy Demonstrated in a Phase 3 Trial**

CheckMate -067 is a Phase 3, double-blind, randomized study that evaluated the *Opdivo + Yervoy* Regimen or *Opdivo* monotherapy vs. *Yervoy* monotherapy in patients with previously untreated advanced melanoma.<sup>1,2</sup> The trial evaluated previously untreated patients, including both *BRAF* V600 mutant and wild-type advanced melanoma, and enrolled 945 patients who 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).<sup>1</sup> Patients were treated until progression or unacceptable toxic effects.<sup>1</sup> The median duration of exposure was 2.8 months (range: 1 day to 18.8 months) for patients in the *Opdivo* + *Yervoy* Regimen arm with a median of four doses (range: 1 to 39 for *Opdivo*; 1 to 4 for *Yervoy*), and 6.6 months (range: 1 day to 17.3 months) duration for the *Opdivo* monotherapy arm with a median of 15 doses (range: 1 to 38).<sup>1,2</sup> The co-primary endpoints were PFS and OS; the study is ongoing and patients continue to be followed for OS.<sup>2</sup>

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 ( $p < 0.0001$ ) vs. *Yervoy* monotherapy.<sup>1</sup> Median PFS was 11.5 months (95% CI: 8.9-16.7) for the *Opdivo* + *Yervoy* Regimen and 6.9 months (95% CI: 4.3-9.5) for *Opdivo* monotherapy, vs. 2.9 months (95% CI: 2.8-3.4) for *Yervoy* monotherapy.<sup>1</sup> The *Opdivo* + *Yervoy* Regimen demonstrated a 58% reduction in the risk of disease progression vs. *Yervoy* (HR: 0.42; 95% CI: 0.34-0.51;  $p < 0.0001$ ), while *Opdivo* monotherapy demonstrated a 43% risk reduction vs. *Yervoy* monotherapy (HR: 0.57; 95% CI: 0.47-0.69;  $p < 0.0001$ ).<sup>1</sup>

In addition, the *Opdivo* + *Yervoy* Regimen and *Opdivo* monotherapy demonstrated higher confirmed objective response rates (ORR; 50% and 40%;  $p < 0.0001$ , respectively) vs. *Yervoy* monotherapy (14%).<sup>1</sup> The percentage of patients with a complete response was 8.9%, 8.5% and 1.9%, favoring the Regimen and *Opdivo* monotherapy over *Yervoy* monotherapy.<sup>1</sup> Partial responses were seen in 41% of patients treated with the *Opdivo* + *Yervoy* Regimen, 31% of patients treated with *Opdivo* monotherapy, and 12% of patients treated with *Yervoy* monotherapy. The *Opdivo* + *Yervoy* Regimen delivered durable responses, with three of four (76%) patients experiencing an ongoing response of at least six months (range: 1.2+ to 15.8+).<sup>1</sup> Of patients in the *Opdivo* monotherapy and *Yervoy* monotherapy arms, 74% and 63% experienced an ongoing response of at least six months, respectively (ranges: 1.3+ to 14.6+; 1.0+ to 13.8+).<sup>1</sup>

“The melanoma community is excited to see the ongoing developments in research from the pharmaceutical industry, including Bristol-Myers Squibb, who made the first approved combination of two Immuno-Oncology treatments available to more patients fighting this

disease,” said Tim Turnham, Executive Director, Melanoma Research Foundation. “Today’s expanded approvals continue to bring new treatment options to patients, and demonstrate the ongoing impact of Immuno-Oncology research.”

In CheckMate -067, serious adverse reactions (73% and 37%), adverse reactions leading to 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* + *Yervoy* arm relative to the *Opdivo* arm.<sup>1</sup> No overall differences in safety or efficacy were reported between elderly and younger patients.<sup>1</sup> The most common adverse reactions leading to discontinuation of the *Opdivo* + *Yervoy* Regimen relative to *Opdivo* as a single-agent were diarrhea (8% and 1.9%), colitis (8% and 0.6%), increased ALT (4.8% and 1.3%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%).<sup>1</sup> The most frequent ( $\geq 10\%$ ) serious adverse reactions in the *Opdivo* + *Yervoy* arm and the *Opdivo* arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%) and pyrexia (10% and 0.6%).<sup>1</sup> The most common adverse reactions ( $\geq 20\%$ ) reported in patients receiving the *Opdivo* + *Yervoy* Regimen relative to *Opdivo* as a single-agent were fatigue (59% and 53%), rash (53% and 40%), diarrhea (52% and 31%), and nausea (40% and 28%).<sup>1</sup> Pyrexia (37%), vomiting (28%) and dyspnea (20%) were also reported in  $\geq 20\%$  of patients receiving the *Opdivo* + *Yervoy* Regimen.<sup>1</sup>

### **About the *Opdivo* + *Yervoy* Regimen**

The scientific rationale for targeting the immune system via dual immune checkpoint inhibition in cancer has formed the basis of a novel approach to the treatment of metastatic melanoma.<sup>2</sup>

Cancer cells may exploit “regulatory” pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack.<sup>2</sup> *Opdivo* and *Yervoy* are immune checkpoint inhibitors that target separate, distinct and complementary checkpoint pathways (PD-1 and CTLA-4).<sup>1</sup> The mechanism of action involves dual immune checkpoint inhibition resulting in increased anti-tumor activity.<sup>1</sup> *Yervoy* blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, while *Opdivo* restores the active T-cell response directed at the tumor.<sup>1,3</sup> This may affect healthy cells and result in immune-mediated adverse reactions, which can be severe and potentially fatal.<sup>1</sup>

Bristol-Myers Squibb has a broad, global development program to study the combination of *Opdivo* and *Yervoy* consisting of more than 14 trials in which more than 2,000 patients have been enrolled worldwide through September 2015.

### **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.<sup>3</sup> *Opdivo*’s broad global development program is based on Bristol-Myers Squibb’s understanding of the biology behind Immuno-Oncology. This scientific expertise serves as the basis for the *Opdivo* development program, which includes a broad range of Phase 3 clinical trials across a variety of tumor types. 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 46 countries including the United States, Japan, and in the European Union.

### **About Metastatic Melanoma**

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin.<sup>3</sup> Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to other organs.<sup>3</sup> The incidence of melanoma has been increasing for at least 30 years.<sup>3</sup> Approximately 73,870 melanoma cases were estimated to be diagnosed in the U.S. in 2015.<sup>3</sup> Melanoma is mostly curable when treated in its early stages.<sup>3</sup> However, in its late stages, 5-year and 10-year survival rates in the U.S. average 15-20% and 10-15%, respectively.<sup>3</sup>

### **About Bristol-Myers Squibb’s Patient Support Programs**

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

## **About Bristol-Myers Squibb's Access Support**

Bristol-Myers Squibb is committed to helping patients access the *Opdivo + Yervoy* Regimen and offers BMS Access Support<sup>®</sup> 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](http://www.bmsaccesssupport.com). For healthcare providers seeking specific reimbursement information, please visit the BMS Access Support Product section by visiting [www.bmsaccesssupportopdivo.com](http://www.bmsaccesssupportopdivo.com).

## **INDICATIONS**

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

OPDIVO<sup>®</sup> (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 demonstration of clinical benefit in confirmatory trials.

OPDIVO<sup>®</sup> (nivolumab), in combination with YERVOY<sup>®</sup> (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 demonstration of clinical benefit in confirmatory trials.

OPDIVO<sup>®</sup> (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<sup>®</sup> (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  $\geq 7$  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 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%).

[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 our social channels:

- Twitter: <https://twitter.com/bmsnews>
- LinkedIn: <https://www.linkedin.com/company/bristol-myers-squibb>
- YouTube: [https://www.youtube.com/channel/UCjFf4oKibYrHae2NZ\\_GPS6g](https://www.youtube.com/channel/UCjFf4oKibYrHae2NZ_GPS6g)

## **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.*

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