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**Encouraging Survival Observed With Opdivo (nivolumab) Plus Yervoy (ipilimumab)  
With Longer Follow-up in First-line Advanced Non-small Cell Lung Cancer,  
in Updated Phase 1b CheckMate -012 Study**

(PRINCETON, N.J., December 5, 2016) – Bristol-Myers Squibb Company (NYSE: BMY) announced updated findings from the Phase 1b trial, CheckMate -012, in chemotherapy-naïve advanced non-small cell lung cancer patients evaluating Opdivo monotherapy, or in combination with Yervoy, at different doses and schedules. Data from this trial have been previously reported. These updated results, with a median follow-up of 16 months, include pooled efficacy findings for the Opdivo and Yervoy combination cohorts (Opdivo 3 mg/kg every two weeks plus Yervoy 1 mg/kg every six [Q6W] or 12 weeks [Q12W]). In the pooled combination cohorts, the median progression-free survival in patients with PD-L1 expression  $\geq 1\%$  (n=46) was 12.7 months (95% CI: 7.8, 23.0) and was not reached in patients with PD-L1 expression  $> 50\%$  (n=13; 95% CI: 7.8, NR). For patients with  $\geq 50\%$  PD-L1 expression (n=13), the one-year overall survival rate was 100% in the pooled combination cohorts. In addition, the confirmed objective response rates in all treated patients (n=77) was 43%, nearly double the response rate reported with Opdivo monotherapy (23%; n=52), with six patients (8%) achieving a complete response, three of which were in patients with PD-L1 expression  $< 1\%$ . The Grade 3/4 treatment-related adverse events were 42% and 31% for the Q12W and Q6W combination cohorts, respectively.

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 Glioblastoma, Small Cell Lung Cancer, Urothelial Cancer, Hepatocellular Carcinoma, Esophageal Cancer, Colorectal Cancer, Gastric 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, unresectable or metastatic renal cell cancer in August 2016 and relapsed or refractory classical Hodgkin lymphoma in December 2016. In addition, ONO has submitted supplemental application for additional indication of Head and Neck Cancer, and is conducting clinical development program including Gastric Cancer, Esophageal Cancer, Gastro-esophageal Junction Cancer and Esophageal Cancer, Small Cell Lung Cancer, Hepatocellular Carcinoma, Glioblastoma, Urothelial Cancer, Malignant Pleural Mesothelioma, Ovarian 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](mailto:public_relations@ono.co.jp)



**Encouraging Survival Observed With *Opdivo* (nivolumab) Plus *Yervoy* (ipilimumab) With Longer Follow-up in First-line Advanced Non-small Cell Lung Cancer, in Updated Phase 1b CheckMate -012 Study**

*In the pooled combination cohorts, median progression-free survival in patients with PD-L1 expression  $\geq 1\%$  was 12.7 months*

*With longer follow-up, the *Opdivo* plus *Yervoy* combination had a safety profile consistent with previous reports of this study*

(PRINCETON, N.J., December 5, 2016) – [Bristol-Myers Squibb Company](#) (NYSE: BMY) announced today updated findings from the Phase 1b trial, CheckMate -012, in chemotherapy-naïve advanced non-small cell lung cancer patients evaluating *Opdivo* monotherapy, or in combination with *Yervoy*, at different doses and schedules. Data from this trial have been previously reported. These updated results, with a median follow-up of 16 months, include pooled efficacy findings for the *Opdivo* and *Yervoy* combination cohorts (*Opdivo* 3 mg/kg every two weeks plus *Yervoy* 1 mg/kg every six [Q6W] or 12 weeks [Q12W]).

In the pooled combination cohorts, the median progression-free survival in patients with PD-L1 expression  $\geq 1\%$  (n=46) was 12.7 months (95% CI: 7.8, 23.0) and was not reached in patients with PD-L1 expression  $\geq 50\%$  (n=13; 95% CI: 7.8, NR). For patients with  $\geq 50\%$  PD-L1 expression (n=13), the one-year overall survival rate was 100% in the pooled combination cohorts. In addition, the confirmed objective response rates in all treated patients (n=77) was 43%, nearly double the response rate reported with *Opdivo* monotherapy (23%; n=52), with six patients (8%) achieving a complete response, three of which were in patients with PD-L1 expression  $< 1\%$ . The Grade 3/4 treatment-related adverse events were 42% and 31% for the Q12W and Q6W combination cohorts, respectively.

Scott N. Gettinger, M.D., associate professor of medicine, Yale Cancer Center, New Haven, Conn., commented, “With longer follow-up in the CheckMate -012 trial, we observe that the *Opdivo* and *Yervoy* combination resulted in encouraging progression-free survival. We are also excited to see the consistent near doubling of response rates with the combination relative to *Opdivo* alone in both PD-L1 expressors and non-expressors, and the previously reported response rates of over 50% and 90%, respectively, among patients with at least 1% and 50% tumor PD-L1 expression. We look forward to further evaluating *Opdivo* plus *Yervoy* in the first line treatment setting for advanced lung cancer.”

Results from CheckMate -012 will be presented today at the International Association for the Study of Lung Cancer 17<sup>th</sup> World Conference on Lung Cancer (WCLC) in Vienna, Austria, during an Oral Session at 11:00 a.m. CET.

Nick Botwood, M.D., development lead, Lung, Bristol-Myers Squibb, commented, “The updated results from CheckMate -012 continue to be promising, and we look forward to advancing the *Opdivo* and *Yervoy* combination in the ongoing CheckMate -227 Phase 3 trial for first-line advanced lung cancer, with the hope of confirming these findings.”

### About CheckMate -012

CheckMate -012 is a multi-arm Phase 1b trial evaluating the safety and tolerability (primary endpoints) of *Opdivo* as monotherapy or in combination with *Yervoy* at different doses and schedules in patients with chemotherapy-naïve advanced non-small cell lung cancer. The secondary endpoints include confirmed objective response rate (ORR) and progression-free survival (PFS) rates at 24 weeks. Exploratory endpoints include overall survival (OS) and efficacy by PD-L1 expression.

The updated data presented at WCLC include a median follow-up of 16 months for the two combination cohorts – *Opdivo* 3 mg/kg every two weeks plus *Yervoy* 1 mg/kg every six weeks (Q6W) (n=39) and 12 weeks (Q12W) (n=38). In the study, both PD-L1 expressors >1% and non-expressors <1% were enrolled. The majority of patients with quantifiable baseline PD-L1 expression in each cohort had PD-L1 tumor expression of  $\geq 1\%$ , including 72% in the Q6W cohort and 70% in the Q12W cohort.

The pooled PFS and OS findings for the combination cohorts in all-treated patients and by tumor PD-L1 expression are reported below.

<b>Nivo 3 Q2W + Ipi 1 Q6/12W</b>	<b>All-Treated (n=77)</b>	<b>PD-L1 <math>\geq 1\%</math> (n=46)</b>	<b>PD-L1 <math>\geq 50\%</math> (n=13)</b>
<b>Median PFS, mo (95%, CI)</b>	8.0 (4.1, 13.2)	12.7 (7.8, 23.0)	NR (7.8, NR)
<b>1-year OS rate, %</b>	76	87	100

Additional efficacy findings were reported for the Q6W and Q12W cohorts in patients with tumor PD-L1 expression  $\geq 1\%$  at WCLC. These findings are summarized below.

	<b>Q12W (n = 23)</b>	<b>Q6W (n = 23)</b>
<b>ORR, % (n/N)</b>	57 (13/23)	57 (13/23)
<b>Median PFS, mo (95%, CI)</b>	10.4 (6.4, NR)	13.2 (3.5, 23.0)
<b>1-year OS rate, %</b>	91	83

The rates of treatment-related adverse events (AEs) with *Opdivo* plus *Yervoy* remained similar to those previously reported. Treatment related AEs of any grade were 84% and 74% for the Q12W and Q6W combination cohorts, respectively. The Grade 3/4 AEs were 42% and 31% for the Q12W and Q6W combination cohorts, respectively. Treatment-related AEs of any grade led to discontinuation in 18% of patients in Q12W and Q6W combination cohorts. Treatment-related Grade 3/4 AEs led to discontinuation in 8% of patients in the Q12W and Q6W combination cohorts.

### **About Lung Cancer**

Lung cancer is the leading cause of cancer deaths globally, resulting in more than 1.5 million deaths each year, according to the World Health Organization. Non-small cell lung cancer (NSCLC) is one of the most common types of the disease and accounts for approximately 85% of cases. About 25% to 30% of all lung cancers are squamous cell carcinomas, and non-squamous NSCLC accounts for approximately 50% to 65% of all lung cancer cases. Survival rates vary depending on the stage and type of the cancer when it is diagnosed. Globally, the five-year survival rate for Stage I NSCLC is between 47% and 50%; for Stage IV NSCLC, the five-year survival rate drops to 2%.

### **Bristol-Myers Squibb: At the Forefront of Immuno-Oncology Science & Innovation**

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational Immuno-Oncology (I-O) medicines that will raise survival expectations in hard-to-treat cancers and will change the way patients live with cancer.

We are leading the scientific understanding of I-O through our extensive portfolio of investigational and approved agents, including the first combination of two I-O agents in metastatic melanoma, and our differentiated clinical development program, which is studying broad patient populations across more than 20 types of cancers with 11 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs uniquely position us to advance the science of combinations across multiple tumors and potentially deliver the next wave of I-O combination regimens with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and inform which patients will benefit most from I-O therapies.

We understand making the promise of I-O a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

### **About Opdivo**

*Opdivo* is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response. By harnessing the body's own immune system to fight cancer, *Opdivo* has become an important treatment option across multiple cancers.

*Opdivo*'s leading global development program is based on Bristol-Myers Squibb's scientific expertise in the field of Immuno-Oncology and includes a broad range of clinical trials across all phases, including Phase 3, in a variety of tumor types. To date, the *Opdivo* clinical development program has enrolled more than 25,000 patients. The *Opdivo* trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from *Opdivo* across the continuum of PD-L1 expression.

In July 2014, *Opdivo* was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. *Opdivo* is currently approved in more than 57 countries, including the United States, the European Union and Japan. In October 2015, the company's *Opdivo* + *Yervoy* combination was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 47 countries, including the United States and the European Union.

### **U.S. FDA APPROVED INDICATIONS FOR OPDIVO®**

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 the confirmatory trials

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

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<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.

OPDIVO<sup>®</sup> (nivolumab) is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO<sup>®</sup> (nivolumab) is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based 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**

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated pneumonitis occurred in 6% (25/407) of patients.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 4.9% (13/263) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 3.4% (9/263) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=8).

### **Immune-Mediated Colitis**

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases.

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**

OPDIVO can cause immune-mediated hepatitis. 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 patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated hepatitis occurred in 13% (51/407) of patients.

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 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**

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and 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. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO with YERVOY, hypophysitis occurred in 9% (36/407) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO with YERVOY, adrenal insufficiency occurred in 5% (21/407) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients.

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO with YERVOY, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with YERVOY. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO with YERVOY, diabetes occurred in 1.5% (6/407) of patients.

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**

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients.

#### **Immune-Mediated Skin Adverse Reactions and Dermatitis**

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated rash occurred in 22.6% (92/407) of patients.

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 Encephalitis**

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and



lumbar puncture. 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 patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one patient receiving OPDIVO with YERVOY (0.2%) after 1.7 months of exposure.

### **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. Across clinical trials of OPDIVO the following clinically significant immune-mediated adverse reactions occurred in <1.0% of patients receiving OPDIVO: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

### **Infusion Reactions**

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. 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 patients receiving OPDIVO monotherapy, infusion-related reactions occurred in 6.4% (127/1994) of patients. In patients receiving OPDIVO with YERVOY, infusion-related reactions occurred in 2.5% (10/407) of patients.

### **Complications of Allogeneic HSCT after OPDIVO**

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

### **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 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). 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 (n=206). 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 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 (n=313) relative to the OPDIVO arm (n=313). 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 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in  $\geq 2\%$  of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, among all patients (safety population [n=263]), adverse reactions leading to discontinuation (4.2%) or to dosing delays (23%) occurred. The most frequent serious adverse reactions reported in  $\geq 1\%$  of patients were infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash and pneumonitis. Ten patients died from causes other than disease progression, including 6 who died from complications of allogeneic HSCT. Serious adverse reactions occurred in 21% of patients in the safety population (n=263) and 27% of patients in the subset of patients evaluated for efficacy (efficacy population [n=95]). In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infections, and sepsis.

### **Common Adverse Reactions**

In Checkmate 037, the most common adverse reaction ( $\geq 20\%$ ) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions ( $\geq 20\%$ )

reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common ( $\geq 20\%$ ) adverse reactions in the OPDIVO plus YERVOY arm (n=313) 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 (n=313) arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 017 and 057, the most common adverse reactions ( $\geq 20\%$ ) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions ( $\geq 20\%$ ) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were asthenic conditions (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, among all patients (safety population [n=263]) and the subset of patients in the efficacy population (n=95), respectively, the most common adverse reactions ( $\geq 20\%$ ) were fatigue (32% and 43%), upper respiratory tract infection (28% and 48%), pyrexia (24% and 35%), diarrhea (23% and 30%), and cough (22% and 35%). In the subset of patients in the efficacy population (n=95), the most common adverse reactions also included rash (31%), musculoskeletal pain (27%), pruritus (25%), nausea (23%), arthralgia (21%), and peripheral neuropathy (21%). In Checkmate 141, the most common adverse reactions ( $\geq 10\%$ ) in patients receiving OPDIVO were cough and dyspnea at a higher incidence than investigator's choice.

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%).

## **Checkmate Trials and Patient Populations**

**Checkmate 067** - advanced melanoma alone or in combination with YERVOY; **Checkmate 037 and 066** - advanced melanoma; **Checkmate 017** - squamous non-small cell lung cancer (NSCLC); **Checkmate 057** - non-squamous NSCLC; **Checkmate 025** - renal cell carcinoma; **Checkmate 205/039** - classical Hodgkin lymphoma; **Checkmate 141** - squamous cell carcinoma of the head and neck.

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

## **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](http://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. Among other risks, there can be no guarantee that the Opdivo plus Yervoy combination will receive regulatory approval for an additional indication. 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.*

### **Contact:**

Bristol-Myers Squibb Company

Media:

Audrey Abernathy, 919-605-4521

[audrey.abernathy@bms.com](mailto:audrey.abernathy@bms.com)

or

Tim Power, 609-252-7509

[timothy.power@bms.com](mailto:timothy.power@bms.com)

Bill Szablewski, 609-252-5894

[william.szablewski@bms.com](mailto:william.szablewski@bms.com)