

April 21, 2016

**First Presentation of Overall Survival Data for *Opdivo*<sup>®</sup> (nivolumab) Shows Significant Survival Benefit at One-Year Versus Investigator's Choice in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck**

(PRINCETON, NJ, April 19, 2016) - Bristol-Myers Squibb Company (NYSE: BMY) announced the first presentation of data from CheckMate -141, a Phase 3 open-label, randomized trial, evaluating Opdivo in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum therapy compared to investigator's choice of therapy (methotrexate, docetaxel, or cetuximab). In the trial, which evaluated overall survival (OS) as the primary endpoint, patients treated with Opdivo experienced a 30% reduction in the risk of death, with a median OS of 7.5 months (95% CI: 5.5-9.1) compared to 5.1 months (95% CI: 4.0-6.0) for investigator's choice (HR=0.70 [97.73% CI: 0.51-0.96] p=0.0101). The one-year survival rate for Opdivo was 36% compared to 16.6% for investigator's choice. The safety profile of Opdivo in CheckMate -141 was consistent with prior studies, with no new safety signals identified.

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.

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**First Presentation of Overall Survival Data for *Opdivo*® (nivolumab) Shows Significant Survival Benefit at One-Year Versus Investigator's Choice in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck**

*Opdivo is the first and only PD-1 inhibitor to demonstrate a statistically significant improvement in overall survival compared to three standard of care options in this setting, based on CheckMate -141*

*Data from CheckMate -141 showed survival benefit with Opdivo in this overall population, regardless of PD-L1 expression or HPV status*

*Safety of Opdivo in CheckMate -141 was consistent with prior studies, with no new safety signals identified*

(PRINCETON, NJ, April 19, 2016) - [Bristol-Myers Squibb Company](#) (NYSE: BMY) announced today the first presentation of data from CheckMate -141, a Phase 3 open-label, randomized trial, evaluating *Opdivo* in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum therapy compared to investigator's choice of therapy (methotrexate, docetaxel, or cetuximab). In the trial, which evaluated overall survival (OS) as the primary endpoint, patients treated with *Opdivo* experienced a 30% reduction in the risk of death, with a median OS of 7.5 months (95% CI: 5.5-9.1) compared to 5.1 months (95% CI: 4.0-6.0) for investigator's choice (HR=0.70 [97.73% CI: 0.51-0.96]  $p=0.0101$ ). The one-year survival rate for *Opdivo* was 36% compared to 16.6% for investigator's choice. The safety profile of *Opdivo* in CheckMate -141 was consistent with prior studies, with no new safety signals identified.

These data were featured today, Tuesday, April 19, during the 2016 Annual Meeting of the American Association for Cancer Research (AACR) official press program at 8:30 A.M. CT and will be presented during the Immuno-Oncology Clinical Trials II Plenary Session from 10:30 A.M. – 12:15 P.M. CT.

Maura Gillison, M.D., Ph.D., lead investigator, Jeg Coughlin Chair of Cancer Research, The Ohio State University Wexner Medical Center, commented, "Squamous cell carcinoma of the head and neck that progresses after platinum-therapy is a devastating disease with a very poor prognosis. There are no systemic therapies that improve survival, and therefore, there is a tremendous unmet need for new treatment options for this patient population. In CheckMate -141, *Opdivo* demonstrated an improvement

in survival compared to three standard of care options in this overall patient population, regardless of PD-L1 expression levels and HPV status.”

Based on a planned interim analysis, this trial was stopped early in January 2016 because an assessment conducted by the independent Data Monitoring Committee concluded the study met its primary endpoint of OS in patients receiving *Opdivo* compared to the control arm.

Jean Viallet, M.D., Global Clinical Research Lead, Oncology, Bristol-Myers Squibb, commented, “We are excited to share, for the first time, data from the CheckMate -141 trial with the oncology community at the 2016 AACR Annual Meeting. We are encouraged by the overall survival results seen with this investigational use of *Opdivo* versus three standard of care options for patients with recurrent or metastatic squamous cell carcinoma of the head and neck, who often face poor survival rates. These findings are supportive of our Immuno-Oncology research goal to study potential treatment options for their ability to help patients with difficult-to-treat cancers achieve long-term survival.”

### **About CheckMate -141**

CheckMate -141 is a Phase 3, open-label, randomized trial evaluating *Opdivo* versus investigator’s choice of therapy in patients with recurrent or metastatic SCCHN with tumor progression within six months of platinum therapy in the adjuvant, primary, recurrent or metastatic setting. Patients were randomized 2:1 to receive *Opdivo* 3 mg/kg intravenously over 60 minutes every two weeks, or one of the following single agents: methotrexate 40 mg/m<sup>2</sup> intravenously weekly, docetaxel 30 mg/m<sup>2</sup> intravenously weekly, or cetuximab 400 mg/m<sup>2</sup> intravenously once then 250 mg/m<sup>2</sup> weekly. Therapies chosen for the control arm represent the most commonly used therapies in the platinum refractory setting. The primary endpoint was OS. Secondary endpoints included objective response rate (ORR) and progression-free survival (PFS). Additional endpoints included safety.

In the trial, patients treated with *Opdivo* experienced a significant reduction (30%) in the risk of death, with a median OS of 7.5 months (95% CI: 5.5-9.1) compared to 5.1 months (95% CI: 4.0-6.0) for the control arm (HR=0.70 [97.73% CI: 0.51-0.96]  $p=0.0101$ ). The one-year OS rate was 36% for *Opdivo* compared to 16.6% for the control arm.

CheckMate -141 also evaluated the efficacy of *Opdivo* by HPV status and PD-L1 expression compared to investigator’s choice of therapy. HPV testing was performed for patients identified by investigators with oropharyngeal tumors. In the study, *Opdivo* demonstrated improved survival in this overall population, regardless of HPV status. HPV-positive status was associated with greater magnitude of effect with *Opdivo* versus investigator’s choice. In HPV-positive patients treated with *Opdivo*, medi-

an OS was 9.1 months vs. 4.4 months for patients treated with investigator’s choice of therapy (HR=0.56 [95% CI: 0.32-0.99]). In HPV-negative patients treated with *Opdivo*, median OS was 7.5 months vs. 5.8 months for patients treated with investigator’s choice of therapy (HR=0.73 [95% CI: 0.42-1.25])

Of randomized patients, 72% (260) were evaluable for PD-L1 expression. Rates of PD-L1 expression were balanced between subgroups. *Opdivo* demonstrated improved survival in the overall population, regardless of PD-L1 expression level (chart below).

**Efficacy Summary: Median Overall Survival by PD-L1 Expression**

	<b>Hazard Ratio (HR) for Opdivo vs. Investigator’s Choice Therapy (Median OS, mos)</b>
<b>&gt;1% PD-L1 expression level</b>	HR=0.55 [95% CI: 0.36-0.83] 8.7 mos vs. 4.6 mos (95% CI: 5.7-9.1) (95% CI: 3.8-5.8)
<b>&lt;1% PD-L1 expression level</b>	HR=0.89 [95% CI: 0.54-1.45] 5.7 mos vs. 5.8 mos (95% CI: 4.4-12.7) (95% CI: 4.0-9.8)

The safety profile of *Opdivo* in CheckMate -141 was consistent with prior studies with no new safety signals identified. Treatment-related adverse events (TRAEs) of any grade occurred in 58.9% of patients on *Opdivo* vs. 77.5% of patients on investigator’s choice. Grade 3-4 TRAEs were reported in 13.1% of patients on *Opdivo* vs. 35.1% of patients on investigator’s choice. Two drug-related deaths were reported as related to *Opdivo* (pneumonitis and hypercalcemia), and one Grade 5 event of lung infection on the investigator’s choice arm.

**About Head & Neck Cancer**

Head and neck cancer is the seventh most common cancer globally, with an estimated 400,000 to 600,000 new cases per year and 223,000 to 300,000 deaths per year. The five-year survival rate is reported as less than 4% for metastatic Stage IV disease. Squamous cell carcinoma of the head and neck (SCCHN) accounts for approximately 90% of all head and neck cancers with global incidence expected to increase by 17% between 2012 and 2022. Risk factors for SCCHN include tobacco and alcohol consumption, and the increasing role of Human Papilloma Virus (HPV) infection leading to rapid increase in oropharyngeal SCCHN in Europe and North America. Quality of life is often impacted for SCCHN

patients as physiological function (breathing, swallowing, eating, drinking), personal characteristics (appearance, speaking, voice), sensory function (taste, smell, hearing), and psychological/social function can be affected.

### **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 choice alongside surgery, radiation, chemotherapy and targeted therapies 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. Our ongoing Immuno-Oncology clinical program is looking at broad patient populations, across multiple solid tumors and hematologic malignancies, and lines of therapy and histologies, with the intent of powering our trials for overall survival and other important measures like durability of response. 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.

We are also investigating other immune system pathways in the treatment of cancer including CTLA-4, CD-137, KIR, SLAMF7, PD-1, GITR, CSF1R, IDO, and LAG-3. These pathways may lead to potential new treatment options – in combination or monotherapy – to help patients fight different types of cancers.

Our collaboration with academia, as well as small and large biotech companies, to research the potential Immuno-Oncology and non-Immuno-Oncology combinations, helps achieve our goal of providing new treatment options in clinical practice.

At Bristol-Myers Squibb, we are committed to changing survival 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) 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**

### **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. Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In Checkmate 037, 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. 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).

### **Immune-Mediated Hepatitis**

Immune-mediated hepatitis can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In Checkmate 037, 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).

### **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 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 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 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 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).

### **Immune-Mediated Nephritis and Renal Dysfunction**

Immune-mediated nephritis can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 increased serum creatinine, withhold and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue. In Checkmate 037, 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 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 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 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 its mechanism of action, OPDIVO 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- containing regimen and for at least 5 months after the last dose of OPDIVO.

## **Lactation**

It is not known whether OPDIVO 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.

## **Serious Adverse Reactions**

In Checkmate 067, serious adverse reactions (37%), adverse reactions leading to permanent discontinuation (14%) or to dosing delays (28%), and Grade 3 or 4 adverse reactions (72%) occurred in the OPDIVO arm. The most frequent ( $\geq 10\%$ ) serious adverse reactions in the OPDIVO arm were diarrhea (2.6%), colitis (1.6%), and pyrexia (0.6%). In Checkmate 037, serious adverse reactions occurred in 41% of pa-

tients 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 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%).

### **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 [www.BMS.com](http://www.BMS.com) or follow us on [LinkedIn](#), [Twitter](#), and [YouTube](#).

## **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 Opdivo will receive regulatory approval for an additional indication in SCCHN. 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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