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**Bristol-Myers Squibb's Opdivo (nivolumab) Receives Expanded FDA Approval  
in Previously-Treated Metastatic Non-Small Cell Lung Cancer (NSCLC),  
Offering Improved Survival to More Patients**

(PRINCETON, NJ, October 9, 2015) – Bristol-Myers Squibb Company (NYSE: BMY) announced that the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) injection, for intravenous use, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR mutation or ALK translocation should have disease progression on appropriate targeted therapy prior to receiving Opdivo.

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. Also, 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. 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: Renal Cell Carcinoma (RCC), 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. In Japan, ONO launched it for the treatment of unresectable melanoma in September 2014. Also, ONO is conducting clinical development programs including RCC, NSCLC, Head and Neck Cancer, Gastric Cancer, Esophageal Cancer, Hepatocellular Carcinoma, Hodgkin Lymphoma, Urothelial Cancer and Glioblastoma.

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) Receives Expanded FDA Approval in Previously-Treated Metastatic Non-Small Cell Lung Cancer (NSCLC), Offering Improved Survival to More Patients**

- *Opdivo is the only PD-1 inhibitor approved for previously treated metastatic squamous and now non-squamous NSCLC patients regardless of PD-L1 expression*<sup>1</sup>
- *Opdivo represents the only PD-1 inhibitor approved by the FDA to deliver superior overall survival compared to chemotherapy, docetaxel, in previously treated metastatic NSCLC*<sup>1</sup>
- *Safety profile of Opdivo is consistent with prior studies*<sup>1</sup>

(PRINCETON, NJ, October 9, 2015) – [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved *Opdivo* (nivolumab) injection, for intravenous use, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR mutation or ALK translocation should have disease progression on appropriate targeted therapy prior to receiving *Opdivo*. In a Phase 3 trial, CheckMate -057, *Opdivo* demonstrated superior overall survival (OS) in previously treated metastatic non-squamous NSCLC compared to chemotherapy, with a 27% reduction in the risk of death (hazard ratio: 0.73 [95% CI: 0.60, 0.89; p=0.0015]), based on a prespecified interim analysis.<sup>1</sup> The median OS was 12.2 months in the *Opdivo* arm (95% CI: 9.7, 15.0) and 9.4 months in the docetaxel arm (95% CI: 8.0, 10.7).<sup>1</sup> This approval expands *Opdivo*'s indication for previously treated metastatic squamous NSCLC to include the non-squamous patient population. Squamous and non-squamous NSCLC together represent approximately 85% to 90% of lung cancer cases.<sup>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.

“Improving survival for cancer patients represents the ultimate goal of treatment,” said Murdo Gordon, senior vice president and head of Worldwide Markets, Bristol-Myers Squibb. “With today’s FDA approval, it is encouraging to know that *Opdivo* will be available to significantly more patients with metastatic NSCLC, helping to improve treatment outcomes for patients who have been previously

treated. We hope that our efforts to bring innovative Immuno-Oncology treatments forward for patients will help increase survivorship and positively impact the lung cancer community.”

This approval is the third for *Opdivo* in the United States this year, and is based on the results of the CheckMate -057 trial, a Phase 3 trial which demonstrated superior OS benefit for *Opdivo* vs. docetaxel in previously treated metastatic NSCLC. *Opdivo* is the only PD-1 therapy to have been studied in a Phase 3 trial of patients with previously treated squamous NSCLC and a separate Phase 3 trial of patients with previously treated non-squamous NSCLC. Biomarker testing is not required for *Opdivo*.

“Non-small cell lung cancer is a difficult to treat disease with high mortality, and patients with squamous and non-squamous NSCLC often respond differently to treatment,” said Dr. Roy Herbst, Chief of Medical Oncology, Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. “*Opdivo* is becoming an important treatment option for more patients with previously treated metastatic NSCLC, and is a welcome addition to our therapy of this disease.”

### **Proven Superior Overall Survival Versus Docetaxel in Metastatic NSCLC**

CheckMate -057 is a landmark, comparative study designed with the goal of demonstrating survival. Clinical results from CheckMate -057 were recently presented at the 2015 European Cancer Congress with simultaneous publication in the *New England Journal of Medicine*. CheckMate -057 is a Phase 3, open-label, randomized clinical trial that evaluated *Opdivo* (3 mg/kg administered intravenously every two weeks) (n=292) vs. docetaxel (75 mg/m<sup>2</sup> administered intravenously every three weeks) (n=290), in patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate targeted therapy may have been given to patients with known EGFR mutation or ALK translocation.<sup>1</sup> This study included patients regardless of their PD-L1 (programmed death ligand-1) expression status. The primary endpoint of this trial was OS.<sup>1</sup>

The median OS was 12.2 months in the *Opdivo* arm (95% CI: 9.7, 15.0) and 9.4 months in the docetaxel arm (95% CI: 8.0, 10.7).<sup>1</sup> The hazard ratio (HR) was 0.73 (95% CI: 0.60, 0.89; p=0.0015), which translates to a 27% reduction in the risk of death with *Opdivo* compared to docetaxel.<sup>1</sup> The prespecified interim analysis was conducted when 413 events were observed (93% of the planned number of events for final analysis).<sup>1</sup> Additional secondary endpoints include investigator-assessed objective response rate (ORR) and progression-free survival (PFS). The ORR in the *Opdivo* arm was 19% (56/292; 4 complete responses, 52 partial responses) (95% CI: 15, 24) and 12% with docetaxel (36/290; 1 complete response, 35 partial responses) (95% CI: 9, 17) p=0.02. The median duration of

response was 17 months in the *Opdivo* arm and 6 months in the docetaxel arm. Median PFS was 2.3 months in the *Opdivo* arm vs. 4.2 months with docetaxel; HR=0.92 (95% CI:0.77, 1.11, p=0.39).

“With today’s announcement, *Opdivo* represents the only PD-1 inhibitor approved for patients regardless of PD-L1 expression, and offers significant improvement over the current standard chemotherapy,” said Michael Giordano, senior vice president, head of Development, Oncology, Bristol-Myers Squibb. “Through our leadership in Immuno-Oncology research, we have taken a comprehensive approach to better understanding and treating metastatic NSCLC, with a primary focus on patients who are in need of new options. We are committed to building upon the promise that *Opdivo* has demonstrated for patients and providing a potential survival benefit in devastating diseases, like metastatic NSCLC.”

The safety profile of *Opdivo* in CheckMate -057 was consistent with prior studies. Serious adverse reactions occurred in 47% of patients receiving *Opdivo*. The most frequent serious adverse reactions in at least 2% of patients receiving *Opdivo* were pneumonia, pulmonary embolism, dyspnea, pleural effusions and respiratory failure. *Opdivo* was discontinued in 13% of patients and was delayed in 29% of patients for an adverse reaction. The most common adverse reactions (reported in  $\geq 20\%$  of patients) were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%) and constipation (23%).<sup>1</sup>

“The approval of *Opdivo* for patients with previously treated metastatic NSCLC represents a major advancement in the way we are able to address the unmet needs of these patients, especially for those who have progressed on prior treatment and, until now, may have had limited options,” said Andrea Ferris, president and chairman of LUNGeivity Foundation. “Bristol-Myers Squibb has shown unwavering commitment to improving survival expectations for patients with metastatic NSCLC and I applaud their work, along with the FDA, in making this treatment option available to more patients.”

Bristol-Myers Squibb has partnered with Dako, an Agilent Technologies company, to develop PD-L1 IHC 28-8 PharmDx, a test which was used to assess PD-L1 expression in the CheckMate -057 trial. This test is now approved by the FDA as a complementary diagnostic, which will provide additional information for physicians. These tests are distinct from companion diagnostics, which are essential for safe and effective use of a drug. Biomarker testing is not required for *Opdivo*.

### **About Lung Cancer**

Lung cancer is one of the leading causes of cancer deaths in the United States.<sup>2</sup> NSCLC is one of the most common types of the disease and accounts for approximately 85% to 90% of lung cancer

cases.<sup>2</sup> Squamous NSCLC accounts for approximately 25% to 30% of all lung cancer cases, while non-squamous NSCLC accounts for approximately 45% to 60% of all lung cancer cases.<sup>2</sup> Survival rates vary depending on the stage and type of the cancer and when it is diagnosed. For Stage IV NSCLC, the five-year survival rate is one percent.<sup>2</sup>

### **About Bristol-Myers Squibb's Patient Support Programs for *Opdivo***

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

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

Bristol-Myers Squibb is committed to helping patients access *Opdivo* and offers numerous programs to support patients and providers in gaining access. BMS Access Support<sup>®</sup>, 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 *Opdivo* specific reimbursement information, please visit the BMS Access Support Product section by visiting [www.bmsaccesssupportopdivo.com](http://www.bmsaccesssupportopdivo.com).

### **About the *Opdivo* Clinical Development Program**

Bristol-Myers Squibb has a broad, global development program to study *Opdivo* in multiple tumor types consisting of more than 50 trials – as monotherapy or in combination with other therapies – in which more than 8,000 patients have been enrolled worldwide.

### **Indication and Important Safety Information for OPDIVO<sup>®</sup> (nivolumab)**

#### **INDICATION**

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.

## **IMPORTANT SAFETY INFORMATION**

### **Immune-Mediated Pneumonitis**

Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred in 0.5% (5/978) of patients receiving OPDIVO as a single agent. In Checkmate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO including five Grade 3, two Grade 2, and three Grade 1 cases. Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold until resolution for Grade 2.

### **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. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon restarting OPDIVO. 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 including three Grade 3, two Grade 2, and two Grade 1 cases..

### **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 OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In Checkmate 057, one patient (0.3%) developed immune-mediated hepatitis.

### **Immune-Mediated Endocrinopathies**

Hypophysitis, adrenal insufficiency, and thyroid disorders can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, and thyroid function prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold OPDIVO 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. Adrenal insufficiency occurred in 1% (n=555) of patients receiving OPDIVO as a single agent. In Checkmate 057, Grade 1 or 2 hypothyroidism, including

thyroiditis, occurred in 7% (20/287) and elevated TSH occurred in 17% of patients receiving OPDIVO. Grade 1 or 2 hyperthyroidism occurred in 1.4% (4/287) of patients.

### **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 OPDIVO and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO. In Checkmate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients.

### **Immune-Mediated Rash**

Immune-mediated rash can occur with OPDIVO treatment. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 rash. . In Checkmate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO including 4 Grade 3 cases.

### **Immune-Mediated Encephalitis**

Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. Across clinical trials of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, <1% of patients were identified as having encephalitis. In Checkmate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO.

### **Other Immune-Mediated Adverse Reactions**

Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone- replacement therapy. The following clinically significant immune-mediated adverse reactions occurred in <2% (n=555) of single-agent OPDIVO-treated patients: uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, and autoimmune neuropathy,. Across clinical trials of OPDIVO as a single agent administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: facial nerve paralysis, motor dysfunction, vasculitis, diabetic ketoacidosis, and myasthenic syndrome.

### **Infusion Reactions**

Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO. In Checkmate 057, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

### **Embryofetal 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 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 OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment.

### **Serious Adverse Reactions**

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.

### **Common Adverse Reactions**

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%).

[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 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 Twitter at <http://twitter.com/bmsnews>.



## **Bristol-Myers Squibb Forward Looking Statement**

*This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2014 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.*

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### **References**

1. Opdivo Prescribing Information. Opdivo U.S. Product Information. Last updated: October 9, 2015. Princeton, NJ: Bristol-Myers Squibb Company.
2. American Cancer Society Web site. "Detailed Guideline: Lung Cancer (Non-Small Cell)." Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf>. Accessed on September 15, 2015.