

March 5, 2015

**FDA Approves Opdivo (nivolumab) for the Treatment of Patients
with Previously Treated Metastatic Squamous Non-Small Cell Lung Cancer**

(PRINCETON, NJ, March 4, 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 squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Opdivo is the first and only PD-1 (programmed death receptor-1) therapy to demonstrate overall survival in previously treated metastatic squamous NSCLC. Opdivo demonstrated significantly superior overall survival (OS) vs. docetaxel, with a 41% reduction in the risk of death, in a prespecified interim analysis of a Phase III clinical trial. The median OS was 9.2 months in the Opdivo arm (95% CI: 7.3, 13.3) and 6 months in the docetaxel arm (95% CI: 5.1, 7.3).

Through the collaboration agreement entered into in September 2011 between ONO and BMS, ONO granted BMS exclusive rights to develop and commercialize Opdivo in the rest of the world, except in Japan, Korea and Taiwan where ONO had retained all rights to develop and commercialize the compound. In July 2014, ONO and BMS signed a new collaboration agreement in which the companies agreed to jointly develop and commercialize Opdivo, ipilimumab and three early-stage immunotherapies in Japan, South Korea and Taiwan.

In USA, Opdivo was approved under accelerated approval for the treatment of unresectable or metastatic melanoma and disease progression following Yervoy[®] (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor in December 2014. Also, BMS has a robust clinical development program in a variety of tumor types overseas, including: Non-Small Cell Lung Cancer (NSCLC), 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, Bladder 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 and Hodgkin Lymphoma.

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



FDA Approves *Opdivo* (nivolumab) for the Treatment of Patients with Previously Treated Metastatic Squamous Non-Small Cell Lung Cancer

Opdivo is the first and only immuno-oncology therapy proven to extend survival in patients treated with one prior therapy

CheckMate -017 achieved the benchmark goal of improving overall survival in previously treated squamous non-small cell lung cancer (NSCLC)

(PRINCETON, NJ, March 4, 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 squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. *Opdivo* is the first and only PD-1 (programmed death receptor-1) therapy to demonstrate overall survival in previously treated metastatic squamous NSCLC. *Opdivo* demonstrated significantly superior overall survival (OS) vs. docetaxel, with a 41% reduction in the risk of death (hazard ratio: 0.59 [95% CI: 0.44, 0.79; p=0.00025]), in a prespecified interim analysis of a Phase III clinical trial. The median OS was 9.2 months in the *Opdivo* arm (95% CI: 7.3, 13.3) and 6 months in the docetaxel arm (95% CI: 5.1, 7.3).

“Bristol-Myers Squibb is committed to patients with lung cancer, and we are pleased to offer *Opdivo* as the first immuno-oncology therapy for patients who have previously treated metastatic squamous NSCLC,” said [Lamberto Andreotti](#), chief executive officer, Bristol-Myers Squibb. “Because lung cancer is one of the most commonly diagnosed cancers in the United States, with high mortality, there is a significant need for treatments that extend survival. We’re thankful to the many patients and healthcare providers that partnered with us to develop a new treatment that has the potential to address that unmet need.”

This approval is the second for *Opdivo* in the United States within three months, and is based on the results of CheckMate -017 and CheckMate -063.

Opdivo is associated with immune-mediated: pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism and hyperthyroidism, other adverse reactions; and embryofetal toxicity. Please see the Important Safety Information section below.

Proven Superior Survival vs. Standard of Care in a Phase III Clinical Trial

CheckMate -017 was a landmark Phase III, open-label, randomized, multinational, multicenter clinical trial that evaluated *Opdivo* (3 mg/kg intravenously over 60 minutes every two weeks) (n=135) vs. standard of care, docetaxel (75 mg/m² intravenously administered every 3 weeks) (n=137), in patients with metastatic squamous NSCLC who had progressed during or after prior platinum doublet-based chemotherapy regimen. This trial included patients regardless of their PD-L1 (programmed death ligand-1) status. The primary endpoint of this trial was overall survival (OS).

In January, the trial was stopped based on an assessment conducted by the independent Data Monitoring Committee (DMC), which concluded that the study met its endpoint, demonstrating superior OS in patients receiving *Opdivo* compared to docetaxel. The prespecified interim analysis was conducted when 199 events (86% of the planned number of events for final analysis) were observed (86 in the *Opdivo* arm and 113 in the docetaxel arm).

Opdivo is the only FDA-approved monotherapy to demonstrate proven superior OS compared to standard of care in more than 15 years in previously treated metastatic squamous NSCLC. The median OS was 9.2 months in the *Opdivo* arm (95% CI: 7.3, 13.3) and 6 months in the docetaxel arm (95% CI: 5.1, 7.3). The hazard ratio was 0.59 (95% CI: 0.44, 0.79; p=0.00025). This hazard ratio translates to a 41% reduction in the risk of death with *Opdivo* compared to docetaxel.

“The FDA approval of *Opdivo* introduces an entirely new treatment modality that has demonstrated unprecedented results for the treatment of previously treated metastatic squamous NSCLC, with the potential to replace chemotherapy for these patients,” said Dr. Suresh Ramalingam, MD, Professor and Director of Medical Oncology, Winship Cancer Institute of Emory University. “This milestone brings to fruition the long-held hope that immuno-oncology medicines can be significantly effective in this difficult-to-treat population.”

About the CheckMate -063 Trial and the Safety Profile of *Opdivo*

The safety profile of *Opdivo* in squamous NSCLC was established in CheckMate -063, a Phase II single-arm, open-label, multinational, multicenter trial of *Opdivo*, administered as a single agent in patients with metastatic squamous NSCLC who have progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen (n=117). Patients received 3 mg/kg of *Opdivo* administered intravenously over 60 minutes every 2 weeks. This trial included patients regardless of their PD-L1 status. The most common adverse reactions (reported in ≥20% of patients) were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%). Serious adverse reactions occurred in 59% of patients

receiving *Opdivo*. The most frequent serious adverse reactions reported in $\geq 2\%$ of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain. *Opdivo* was discontinued due to adverse reactions in 27% of patients. Twenty-nine percent of patients receiving *Opdivo* had a drug delay for an adverse reaction.

With at least 10 months of minimum follow up for all patients, the confirmed objective response rate (ORR), the study's primary endpoint, was 15% (17/117) (95% CI = 9, 22) of which all were partial responses. The median time to onset of response was 3.3 months (range: 1.7 to 8.8 months) after the start of *Opdivo* treatment. Seventy-six percent of *Opdivo* responders (13/17 patients) had ongoing responses with durability of response ranging from 1.9+ to 11.5+ months; 10 of these 17 (59%) patients had durable responses of 6 months or longer.

"The approval of *Opdivo* for the treatment of previously treated metastatic squamous non-small cell lung cancer is a major advancement in delivering extended survival for patients fighting this deadly disease," said Andrea Ferris, President and Chairman, Lungevity Foundation. "We are very excited for an immuno-oncology therapy to enter the market and offer options and hope for many of our patients. I applaud the FDA and Bristol-Myers Squibb for their work in making this important and first of its kind treatment available to patients so quickly."

About Lung Cancer

Lung cancer is one of the leading causes of cancer deaths in the United States. NSCLC is one of the most common types of the disease and accounts for approximately 85 percent of cases. Squamous cell NSCLC accounts for approximately 25 to 30 percent of all lung cancers. 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.

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®, 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. For healthcare providers seeking *Opdivo* specific reimbursement information, please visit the BMS Access Support Product section by visiting 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 7,000 patients have been enrolled worldwide.

Indication and Important Safety Information for OPDIVO® (nivolumab)

INDICATION

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis

- Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO; no cases occurred in Trial 3. In Trial 3, immune-mediated pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO including five Grade 3 and two Grade 2 cases. Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold OPDIVO until resolution for Grade 2.

Immune-Mediated Colitis

- In Trial 3, diarrhea occurred in 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated colitis occurred in 0.9% (1/117) of patients. Monitor patients for immune-mediated colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3. Permanently discontinue OPDIVO for Grade 4 colitis or recurrent colitis upon restarting OPDIVO.

Immune-Mediated Hepatitis

- In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). 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 OPDIVO for Grade 3 or 4 immune-mediated hepatitis.

Immune-Mediated Nephritis and Renal Dysfunction

- In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 serum creatinine elevation, 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.

Immune-Mediated Hypothyroidism and Hyperthyroidism

- In Trial 3, hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. Hyperthyroidism occurred in 1.7% (2/117) of patients including one Grade 2 case. Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred in <2% of OPDIVO-treated patients: adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction and vasculitis. Across clinical trials of OPDIVO administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome. Based on the severity of adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy.

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 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, advise women to discontinue breastfeeding during treatment.

Serious Adverse Reactions

- In Trial 3, serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse drug reactions reported in $\geq 2\%$ of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Common Adverse Reactions

- The most common adverse reactions ($\geq 20\%$) reported with OPDIVO in Trial 3 were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%).

Please see U.S. Full Prescribing Information for OPDIVO [here](#).

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 or follow us on Twitter at <http://twitter.com/bmsnews>.

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Contacts:

Media: Carrie Fernandez, 609-419-5448, cell 215-859-2605, carrie.fernandez@bms.com
Chrissy Trank, 609-419-5497, cell 732-551-5343, christina.trank@bms.com

Investors: John Elicker, 609-252-4611, john.ellicker@bms.com
Ranya Dajani, 609-252-5330, ranya.dajani@bms.com