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European Commission Approves Nivolumab BMS, the First PD-1 Immune Checkpoint Inhibitor in Europe Proven to Extend Survival for Patients with Previously-Treated Advanced Squamous Non-Small Cell Lung Cancer

(PRINCETON, NJ, July 20, 2015)– Bristol-Myers Squibb Company (NYSE: BMY) announced that the European Commission has approved Nivolumab BMS for the treatment of locally advanced or metastatic squamous (SQ) non-small cell lung cancer (NSCLC) after prior chemotherapy. This approval marks the first major treatment advance in SQ NSCLC in more than a decade in the European Union (EU). Nivolumab is also the first and only PD-1 immune checkpoint inhibitor to demonstrate overall survival (OS) in previously-treated metastatic SQ NSCLC. This approval allows for the marketing of nivolumab in all 28 Member States of the EU.

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 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. In EU, Opdivo was approved for the treatment of advanced (unresectable or metastatic) melanoma in adults regardless of BRAF status in June 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, 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, Hepatocellular Carcinoma and Hodgkin Lymphoma.

Attached from the following page is the press release made by BMS for your information.

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European Commission Approves Nivolumab BMS, the First PD-1 Immune Checkpoint Inhibitor in Europe Proven to Extend Survival for Patients with Previously-Treated Advanced Squamous Non-Small Cell Lung Cancer

First Immuno-Oncology agent approved in Europe for lung cancer, and the first major treatment advance in more than a decade

Approval based on Checkmate -017, which demonstrated nivolumab doubled overall survival versus chemotherapy (42% vs. 24%), and showed a 41% reduction in the risk of death versus docetaxel; file also included data from CheckMate -063

Safety profile of nivolumab is consistent with previously-reported trials

(PRINCETON, NJ, July 20, 2015 – [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced that the European Commission has approved Nivolumab BMS for the treatment of locally advanced or metastatic squamous (SQ) non-small cell lung cancer (NSCLC) after prior chemotherapy. This approval marks the first major treatment advance in SQ NSCLC in more than a decade in the European Union (EU). Nivolumab is also the first and only PD-1 immune checkpoint inhibitor to demonstrate overall survival (OS) in previously-treated metastatic SQ NSCLC. This approval allows for the marketing of nivolumab in all 28 Member States of the EU.

“With the EU approval of nivolumab, patients in Europe have for the first time in more than ten years access to an entirely new treatment modality for advanced squamous non-small cell lung cancer, which has the potential to replace the current standard of care,” said [Emmanuel Blin](#), senior vice president, head of commercialization, policy and operations, Bristol-Myers Squibb. “Bristol-Myers Squibb is passionate about changing survival expectations and the way patients live with advanced cancers, and is committed to continually deliver, with speed and urgency, new approaches to pursue this goal.”

Approval is based on the results of CheckMate -017 and -063. In the Phase III CheckMate -017 study, nivolumab demonstrated superior clinical benefit across all endpoints versus docetaxel, the standard of care, regardless of PD-L1 (programmed death ligand-1) expression status, including a 41% reduction in the risk of death, significantly superior OS rate of 42% versus 24% for docetaxel at one-year and superior durable antitumor activity. In the Phase II CheckMate -063 study, nivolumab showed an estimated 41% one-year survival rate and a median OS of 8.2 months. The safety profile of

nivolumab is consistent with previously reported trials, and in Checkmate -017, is also favorable compared to docetaxel.

“Today’s approval of nivolumab for squamous non-small cell lung cancer is truly a major advance for patients fighting this devastating disease, and the providers that treat them,” said Rolf Stahel, MD, president of the European Society of Medical Oncology and Professor at University Hospital Zurich. “Nivolumab has shown statistically significant and clinically meaningful improvement in efficacy versus standard of care in this patient population. This approval reinforces the science behind Immuno-Oncology including our understanding of the role of PD-L1 expression.”

In Europe, incidence and mortality rates for lung cancer are on the rise, currently accounting for 20% of all cancer deaths. NSCLC is one of the most common types of the disease and accounts for approximately 85% of lung cancer cases. SQ NSCLC accounts for approximately 25% to 30% of all lung cancers. For patients with NSCLC, whose disease reoccurs or progresses despite chemotherapy, the treatment options are limited and the prognosis is poor, with a five-year survival rate of approximately 2%, globally.

About CheckMate -017, -063

The European Commission’s approval is based on data from two studies (Phase III CheckMate -017 and Phase II CheckMate -063). Together, the trials investigated nivolumab at a dose of 3 mg/kg every two weeks, which has been well-established across the Phase III nivolumab clinical development program for various tumors.

CheckMate -017 is a landmark Phase III, open-label, randomized clinical trial that evaluated nivolumab 3mg/kg intravenously over 60 minutes every two weeks versus standard of care, docetaxel 75 mg/m² intravenously administered every three weeks in patients with advanced SQ NSCLC who had progressed during or after one prior platinum doublet-based chemotherapy regimen. The study’s primary endpoint was OS and secondary endpoints included progression-free survival (PFS) and overall response rate (ORR). The trial included patients regardless of their PD-L1 expression status.

Results from CheckMate -017 showed a 41% reduction in the risk of death with a one-year survival rate of 42% for nivolumab (42.1% [95% CI: 33.7, 50.3]) versus 24% (23.7% [95% CI: 16.9, 31.1]) for docetaxel (HR 0.59, 96.8% CI: 0.43, 0.81; p=0.0002). Median OS was 9.2 months versus 6 months for nivolumab and docetaxel, respectively. Nivolumab also demonstrated consistent, statistically significant and clinically meaningful improvements across secondary endpoints, ORR and PFS, versus docetaxel in patients with previously treated advanced SQ NSCLC. Survival benefit was observed independent of PD-L1 expression across all pre-specified expression levels (1%, 5% and 10%).

The safety profile of nivolumab in CheckMate -017 was consistent with prior studies and favorable versus docetaxel. Treatment-related adverse events (AEs) occurred less frequently with nivolumab (any grade, 58%; grade 3-4, 6.9%; no grade 5 events) than docetaxel (any grade, 86%; grade 3-5, 55%; grade 5, 2.3%), including both hematology and non-hematology toxicities. Treatment-related AEs led to discontinuation in 3.1% of patients in the nivolumab arm compared to 10.1% for docetaxel. Pneumonitis (1.5%) was the most common treatment-related AE leading to discontinuation in the nivolumab arm and peripheral neuropathy (3.1%) for the docetaxel arm.

Findings from CheckMate -017 were recently published in [*The New England Journal of Medicine*](#) and presented during an oral abstract session at the 2015 American Society of Clinical Oncology Annual Meeting in May 2015.

CheckMate -063 is a Phase II, single-arm, open-label trial that included patients with metastatic SQ NSCLC who had progressed after two or more lines of therapy. In this trial, the confirmed objective response rate by an independent radiology review committee, the study's primary endpoint, was 14.5% (95% CI: 8.47, 22.2) with an estimated one-year survival rate of 41% and median OS of 8.21 months (95% CI: 6.05, 10.9). The safety profile of nivolumab in CheckMate -063 was consistent with prior clinical studies and managed using established treatment algorithms.

About Nivolumab

Bristol-Myers Squibb submitted two separate Marketing Authorization Applications, one in advanced melanoma under the tradename *Opdivo* and one for squamous NSCLC under the Nivolumab BMS tradename in order to accelerate availability of nivolumab for health care professionals in both indications. The goal is to have these two marketing authorizations "reconciled" into a single marketing authorization, under the *Opdivo* brand name toward the end 2015.

Bristol-Myers Squibb has a broad, global development program with over 8,000 patients enrolled in more than 50 trials evaluating nivolumab across multiple tumor types – as monotherapy or in combination with other therapies.

Nivolumab is the first PD-1 immune checkpoint inhibitor to receive regulatory approval on July 4, 2014 when Ono Pharmaceutical Co. announced that it received manufacturing and marketing approval in Japan for the treatment of patients with unresectable melanoma. On December 22, 2014, the U.S. Food and Drug Administration (FDA) granted its first approval for nivolumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following *Yervoy* (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor. On March 4, 2015, nivolumab received its second FDA approval for the treatment of patients with metastatic squamous non-small cell

lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. The European Commission announced approval of nivolumab on June 19, 2015, for the treatment of advanced (unresectable or metastatic) melanoma in adults, regardless of BRAF status.

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 1 or Trial 3. In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis occurred in 2.2% (6/268) of patients receiving OPDIVO; one with Grade 3 and five with Grade 2. 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 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis occurred in 2.2% (6/268) of patients receiving OPDIVO; five with Grade 3 and one with Grade 2. 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 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs 12%), alkaline phosphatase (22% vs 13%), ALT (16% vs 5%), and total bilirubin (9% vs 0). Immune-mediated hepatitis occurred in 1.1% (3/268) of patients receiving OPDIVO; two with Grade 3 and one with Grade 2. 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 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients. 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 1, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of

patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. 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

- In Trial 1 and 3 (n=385), 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 1, serious adverse reactions occurred in 41% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.
- In 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 1 were rash (21%) and 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.

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. NSCLC is one of the most common types of the disease and accounts for approximately 85 percent of cases. Survival rates vary depending on the stage, histology and sub-type of lung cancer. The majority of NSCLC patients have advanced stage

disease at the time of diagnosis. Globally, the five-year survival rate for Stage I NSCLC is between 47 and 50 percent; for Stage IV NSCLC, the five-year survival rate drops to two percent.

Lung cancer has the highest economic burden of all cancers in the European Union, costing an estimated €18.8 billion or 15 percent of overall cancer costs.

Immuno-Oncology at Bristol-Myers Squibb

Surgery, radiation, cytotoxic or targeted therapies have represented the mainstay of cancer treatment over the last several decades, but long-term survival and a positive quality of life have remained elusive for many patients with advanced disease.

To address this unmet medical need, Bristol-Myers Squibb is leading research in an innovative field of cancer research and treatment known as Immuno-Oncology, which involves agents whose primary mechanism is to work directly with the body's immune system to fight cancer. The company is exploring a variety of compounds and immunotherapeutic approaches for patients with different types of cancer, including researching the potential of combining Immuno-Oncology agents that target different pathways in the treatment of cancer.

Bristol-Myers Squibb is committed to advancing the science of Immuno-Oncology, with the goal of changing survival expectations and the way patients live with cancer.

About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical, Bristol-Myers Squibb expanded its territorial rights to develop and commercialize nivolumab globally except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Bristol-Myers Squibb and Ono Pharmaceutical further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global pharmaceutical 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>.

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 nivolumab will be a commercially successful product. 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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