

April 13, 2016

European Commission Approves Expanded Use of *Opdivo*[®] (nivolumab) to Include Previously Treated Metastatic Non-Squamous Non-Small Cell Lung Cancer

(PRINCETON, NJ, April 6, 2016) – Bristol-Myers Squibb Company (NYSE: BMY) announced that the European Commission has approved Opdivo (nivolumab) monotherapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. Opdivo is the only approved PD-1 inhibitor to demonstrate superior overall survival (OS) in two separate Phase 3 trials in previously treated metastatic NSCLC; one trial in squamous NSCLC (CheckMate -017) and the other in non-squamous NSCLC (CheckMate -057), the basis of this approval. Together, these trials confirm the benefit of Opdivo for patients with previously treated metastatic NSCLC, regardless of PD-L1 expression. The approval allows for the expanded marketing of Opdivo in previously treated metastatic NSCLC in all 28 Member States of the European Union.

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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European Commission Approves Expanded Use of *Opdivo*[®] (nivolumab) to Include Previously Treated Metastatic Non-Squamous Non-Small Cell Lung Cancer

This approval expands Opdivo's existing lung cancer indication in previously treated metastatic squamous NSCLC to include the non-squamous patient population, which together represents 85% of lung cancer cases

Opdivo is the only PD-1 inhibitor approved for a broad range of patients with previously treated metastatic NSCLC, regardless of PD-L1 expression

Opdivo represents the first and only approved PD-1 inhibitor to demonstrate superior overall survival compared to docetaxel, in previously treated metastatic NSCLC

(PRINCETON, NJ, April 6, 2016) – [Bristol-Myers Squibb Company](#) (NYSE: BMY) announced today that the European Commission has approved *Opdivo* (nivolumab) monotherapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. *Opdivo* is the only approved PD-1 inhibitor to demonstrate superior overall survival (OS) in two separate Phase 3 trials in previously treated metastatic NSCLC; one trial in squamous NSCLC (CheckMate -017) and the other in non-squamous NSCLC (CheckMate -057), the basis of this approval. Together, these trials confirm the benefit of *Opdivo* for patients with previously treated metastatic NSCLC, regardless of PD-L1 expression. The approval allows for the expanded marketing of *Opdivo* in previously treated metastatic NSCLC in all 28 Member States of the European Union.

Emmanuel Blin, senior vice president, Head of Commercialization, Policy and Operations, Bristol-Myers Squibb, commented, “At Bristol-Myers Squibb, our goal is to help improve survival outcomes for patients with hard-to-treat cancers, such as advanced non-small cell lung cancer. Today’s approval is indicative of our commitment to bringing our Immuno-Oncology science and the potential for long-term survival to a broader range of lung cancer patients in Europe. *Opdivo* is the only PD-1 inhibitor approved in Europe to have demonstrated, in two separate Phase 3 trials, a significant survival advantage in this patient population, offering a much-needed new treatment option to patients fighting this disease.”

The approval is based on the results of Phase 3 trial, CheckMate -057, which were published in [The New England Journal of Medicine](#). In CheckMate -057, *Opdivo* was evaluated in patients with metastatic non-squamous NSCLC compared to docetaxel, and included patients regardless of PD-L1 expression. *Opdivo* demonstrated superior OS compared to docetaxel, with a 27% reduction in the risk

of death (HR: 0.73 [95% CI: 0.59-0.89; $p=0.0015$]) with a one-year survival rate of 51% for *Opdivo* (95% CI: 44.6-56.1) versus 39% for docetaxel (95% CI: 33.3-44.6). Biomarker testing for PD-L1 expression is not required with *Opdivo*. The Summary of Product Characteristics (SmPC) notes that physicians should consider the delayed onset of *Opdivo* effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within the first 3 months was observed with *Opdivo* compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumor PD-L1 expression.

Luis Paz-Ares, MD, Hospital Universitario Doce de Octubre, Madrid, Spain, commented, “Today’s approval expands the availability of *Opdivo* as a treatment option for a broader range of lung cancer patients – previously treated metastatic squamous and now non-squamous non-small cell lung cancer – which represents the majority of diagnosed lung cancer cases. As the only approved PD-1 inhibitor proven to have demonstrated a survival benefit versus a standard of care, regardless of PD-L1 expression, healthcare providers can offer treatment with *Opdivo* to appropriate patients who have received prior chemotherapy without the need to first conduct biomarker testing to determine PD-L1 expression. This approval is meaningful news for patients and their families who are in need of new treatment options.”

Proven Superior Overall Survival Versus Docetaxel in Previously Treated Metastatic NSCLC

CheckMate -057 is an open-label, randomized Phase 3 study, which evaluated *Opdivo* versus docetaxel in patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with overall survival (OS) as the primary endpoint. Objective response rate (ORR) and progression-free survival (PFS) were evaluated as secondary endpoints. This study included patients regardless of PD-L1 expression level. In the study, patients were randomized to receive *Opdivo* (3 mg/kg administered intravenously every two weeks) versus docetaxel (75 mg/m² administered intravenously every three weeks). The prespecified interim analysis was conducted when 413 events were observed (93% of the planned number of events for final analysis).

Opdivo demonstrated superior OS in previously treated metastatic non-squamous NSCLC compared to docetaxel, with a 27% reduction in the risk of death (HR: 0.73 [95% CI: 0.59-0.89; $p=0.0015$]) with a one-year survival rate of 51% for *Opdivo* (95% CI: 44.6-56.1) compared to 39% for docetaxel (95% CI: 33.3-44.6). The median OS was 12.2 months in patients receiving *Opdivo* (95% CI: 9.66-14.98) and 9.4 months with docetaxel (95% CI: 8.0-10.68). 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, $p=0.0246$). For patients administered *Opdivo*, median duration of response was 17.2 months and 5.6 months for docetaxel. Median PFS was 2.3 months for *Opdivo* versus 4.2 months for docetaxel (HR: 0.92 [95% CI: 0.77-1.11, $p=0.3932$]).

Results of a post-hoc, exploratory multivariate analysis conducted in support of the SmPC development, indicated that *Opdivo*-treated patients with poorer prognostic features and/or aggressive disease when combined with low or no tumor PD-L1 expression may be at higher risk of death within the first 3 months [*Opdivo* arm [59/292, 20.2%] as compared to the docetaxel arm [44/290, 15.2%]). There were no early deaths due to study drug toxicity in either arm.

The safety profile of *Opdivo* in CheckMate -057 was consistent with prior studies. Serious adverse reactions occurred in 47% of patients receiving *Opdivo*. In the overall patient population, 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 in patients treated with *Opdivo* (reported in >20% of patients) were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%) and constipation (23%).

The PD-L1 IHC 28-8 PharmDx, a test which was used to assess PD-L1 expression in the CheckMate -057 trial, is now Conformité Européene (CE) marked in Europe, and can be used to provide additional information for physicians. PD-L1 testing is not required to initiate *Opdivo* treatment for locally advanced or metastatic NSCLC patients.

CheckMate -017 is a landmark, Phase 3, open-label, randomized clinical trial that evaluated *Opdivo* 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 squamous 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 PFS and 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 *Opdivo* (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 *Opdivo* and docetaxel, respectively. *Opdivo* also demonstrated consistent, statistically significant and clinically meaningful improvements across secondary endpoints, ORR and PFS, versus docetaxel in patients with previously treated advanced squamous NSCLC. Survival benefit was observed regardless

of PD-L1 expression across all pre-specified expression levels (1%, 5% and 10%). The safety profile of *Opdivo* in CheckMate -017 was consistent with prior studies. Findings from CheckMate -017 were published in [*The New England Journal of Medicine*](#) and presented at the 2015 American Society of Clinical Oncology Annual Meeting.

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% 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 & 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 OS 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 of 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 OS 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 48 countries including the United States, Japan, and in the European Union.

U.S. FDA APPROVED INDICATIONS

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.

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 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).

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 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).

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 057, one patient (0.3%) developed immune-mediated hepatitis.

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 057, 0.3% (1/287) of OPDIVO-treated patients developed adrenal insufficiency. 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.

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 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients receiving OPDIVO.

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 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO including four 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. 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 057, Grade 2 infusion reactions requiring corticosteroids occurred in 1.0% (3/287) of patients receiving OPDIVO.

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 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%).

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 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. 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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