U.S. Food and Drug Administration Approves Opdivo® (nivolumab) for the Treatment of Patients with Advanced Esophageal Squamous Cell Carcinoma (ESCC) After Prior Fluoropyrimidine- and Platinum-based Chemotherapy

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Opdivo demonstrated superior overall survival benefit compared to docetaxel or paclitaxel

First approved immunotherapy in this patient population regardless of tumor PD-L1 expression level

PRINCETON, N.J.--(BUSINESS WIRE)—Bristol Myers Squibb (NYSE: BMY) today announced that Opdivo® (nivolumab) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. This application was granted Priority Review Designation by the FDA, and the approval is based on the Phase 3 ATTRACTION-3 trial in which Opdivo (n=210) demonstrated superior overall survival (OS) versus taxane chemotherapy (n=209) (investigator’s choice of docetaxel or paclitaxel) (hazard ratio [HR] 0.77; 95% confidence interval [CI]: 0.62 to 0.96; p=0.0189). The median OS was 10.9 months (95% CI: 9.2 to 13.3) for Opdivo compared to 8.4 months (95% CI: 7.2 to 9.9) for docetaxel or paclitaxel. Opdivo is the first approved immunotherapy in this setting regardless of tumor PD-L1 expression level.

Opdivo is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when Opdivo is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials. Please see the Important Safety Information section below.

“Many cases of esophageal cancer are diagnosed at the advanced stage, when the disease could have a significant impact on a patient’s health.” said Adam Lenkowsky, general manager and head, U.S., Oncology, Immunology, Cardiovascular, Bristol Myers Squibb. “The approval of Opdivo as a new treatment option for previously treated patients with advanced esophageal squamous cell carcinoma, regardless of PD-L1 expression, highlights our commitment to providing new options to address the unmet needs of patients and brings us another step closer to understanding the full potential of immunotherapy for gastrointestinal cancers.”

About ATTRACTION-3

ATTRACTION-3 (NCT02569242) is a Phase 3, multicenter, randomized, active-controlled, open-label global study evaluating Opdivo versus taxane chemotherapy (investigator’s choice of docetaxel or paclitaxel) in patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma, refractory or intolerant to at least one prior fluoropyrimidine- and platinum-based regimen. The trial included patients regardless of tumor PD-L1 status, but tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory.

The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants or had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients were randomized to receive Opdivo 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=210)
or investigator's choice of taxane chemotherapy (n=209) of either docetaxel 75 mg/m² intravenously every 3 weeks (n=65), or paclitaxel 100 mg/m² intravenously once a week for 6 weeks followed by 8 weeks of treatment (n=144). Patient enrollment occurred predominantly in Asia, with the United States and Europe accounting for the remainder. Patients were treated until disease progression, assessed by the investigator or Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), or unacceptable toxicity. The major efficacy outcome measure was OS. Additional efficacy outcome measures included overall response rate (ORR) and progression-free survival (PFS) as assessed by the investigator using RECIST v1.1 and duration of response (DOR). There was no statistically significant difference between the two arms for ORR (19.3% [33/171, 95% CI: 13.7 to 26.0] versus 21.5% [34/158, 95% CI: 15.4 to 28.8] for Opdivo, 0.6% complete response [CR] and 18.7% partial response [PR]) and investigator's choice chemotherapy (1.3% CR and 20.3% PR), respectively; p=0.6323. The median PFS was 1.7 months (95% CI: 1.5 to 2.7) for Opdivo versus 3.4 months (95% CI: 3.0 to 4.2) for investigator's choice chemotherapy (HR 1.1; 95% CI: 0.9 to 1.3), however it was not tested with the pre-specified hierarchical testing strategy. This trial was sponsored by Ono Pharmaceutical Co. Ltd. of Japan, Bristol-Myers Squibb's development partner for Opdivo.

**Select Safety Profile from ATTRACTION-3**

The safety of Opdivo was evaluated in ATTRACTION-3 in 209 patients. Serious adverse reactions occurred in 38% of patients receiving Opdivo. Serious adverse reactions reported in ≥2% of patients who received Opdivo were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The following fatal adverse reactions occurred in patients who received Opdivo: interstitial lung disease or pneumonitis (2%), pneumonia (1%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%). Opdivo was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction. The most common adverse reactions occurring in ≥20% of Opdivo-treated patients were rash (22%) and decreased appetite (21%).

**About Esophageal Cancer**

In the United States, it is estimated that approximately 18,440 new cases of esophageal cancer will be diagnosed and approximately 16,170 deaths will result from the disease this year alone. Esophageal cancer is a type of gastrointestinal cancer that starts in the inner layer of the esophagus (the mucosa) and grows. The mucosa is normally lined with squamous cells, and cancer starting in these cells is called squamous cell carcinoma, and accounts for less than 30% of esophageal cancers in the United States. For about 25% of patients, the disease is diagnosed in the advanced stage, which is typically harder to treat.

**Indication**

OPDIVO® (nivolumab) is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

The recommended dosage of OPDIVO for this indication is 240 mg IV infusion over 30 minutes every 2 weeks or 480 mg IV infusion over 30 minutes every 4 weeks, until disease progression or unacceptable toxicity. OPDIVO (10 mg/mL) is an injection for intravenous (IV) use.

**IMPORTANT SAFETY INFORMATION**

**Immune-Mediated Pneumonitis**

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients.

**Immune-Mediated Colitis**

OPDIVO can cause immune-mediated colitis. 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 monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

**Immune-Mediated Hepatitis**

OPDIVO can cause immune-mediated hepatitis. 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. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients.

**Immune-Mediated Endocrinopathies**
OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and 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. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hypothyroidism.

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients.

**Immune-Mediated Nephritis and Renal Dysfunction**

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients.

**Immune-Mediated Skin Adverse Reactions**

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients.

**Immune-Mediated Encephalitis**

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRL and lumbar puncture. 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 patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids.

**Other Immune-Mediated Adverse Reactions**

Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypophysitis, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

**Infusion-Related Reactions**

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

**Embryo-Fetal Toxicity**

Based on 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.

**Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone**

In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**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 not to...
breastfeed during treatment and for at least 5 months after the last dose.

**Serious Adverse Reactions**

In Attraction-3, serious adverse reactions occurred in 38% of patients receiving OPDIVO (n=209). Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%).

**Common Adverse Reactions**

In Attraction-3, the most common adverse reactions occurring in ≥20% of OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%).

Please see U.S. Full Prescribing Information for OPDIVO.

**Bristol Myers Squibb: Advancing Cancer Research**

At Bristol Myers Squibb, patients are at the center of everything we do. The goal of our cancer research is to increase patients’ quality of life, long-term survival and make cure a possibility. We harness our deep scientific experience, cutting-edge technologies and discovery platforms to discover, develop and deliver novel treatments for patients.

Building upon our transformative work and legacy in hematology and Immuno-Oncology that has changed survival expectations for many cancers, our researchers are advancing a deep and diverse pipeline across multiple modalities. In the field of immune cell therapy, this includes registrational CAR T cell agents for numerous diseases, and a growing early-stage pipeline that expands cell and gene therapy targets, and technologies. We are developing cancer treatments directed at key biological pathways using our protein homeostasis platform, a research capability that has been the basis of our approved therapies for multiple myeloma and several promising compounds in early- to mid-stage development. Our scientists are targeting different immune system pathways to address interactions between tumors, the microenvironment and the immune system to further expand upon the progress we have made and help more patients respond to treatment. Combining these approaches is key to delivering potential new options for the treatment of cancer and addressing the growing issue of resistance to immunotherapy. We source innovation internally, and in collaboration with academia, government, advocacy groups and biotechnology companies, to help make the promise of transformational medicines a reality for patients.

**About Bristol Myers Squibb’s Patient Access Support**

Bristol Myers Squibb remains committed to providing assistance so that cancer patients who need our medicines can access them and expedite time to therapy.

BMS Access Support®, the Bristol Myers Squibb patient access and reimbursement program, is designed to help appropriate patients initiate and maintain access to BMS medicines during their treatment journey. BMS Access Support offers benefit investigation, prior authorization assistance, as well as co-pay assistance for eligible, commercially insured patients. More information about our access and reimbursement support can be obtained by calling BMS Access Support at 1-800-861-0048 or by visiting www.bmsaccesssupport.com.

**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, Ono and Bristol Myers Squibb 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 BMS.com or follow us on LinkedIn, Twitter, YouTube, Facebook and Instagram.

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol-Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

**Cautionary Statement Regarding Forward-Looking Statements**

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, whether Opdivo for the additional indication described in this release will be commercially successful and that continued approval of such product candidate for such additional indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that
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affect Bristol Myers Squibb's business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

References


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#FDA approves $BMY therapy for certain previously treated patients with advanced esophageal squamous cell carcinoma