Bristol-Myers Squibb Receives FDA Approval for Opdivo (nivolumab) in MSI-H or dMMR Metastatic Colorectal Cancer That Has Progressed Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

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PRINCETON, N.J.

- Approval based on CheckMate -142, in which Opdivo demonstrated an objective response rate of 28% (95% CI: 17-42; 15/53) among patients who received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) injection for intravenous use for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Approval for this indication has been granted under accelerated approval based on overall response rate (ORR) and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. The recommended dose is 240 milligrams administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity.

Approval Based on Notable Tumor Response Rate and Duration of Response

CheckMate -142 is a Phase 2, multicenter, open-label, single-arm study evaluating Opdivo in patients with locally determined...
dMMR or MSI-H mCRC whose disease had progressed during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy.\textsuperscript{1,2} In this study, 74 patients received Opdivo 3 mg/kg administered intravenously every two weeks.\textsuperscript{2} The recommended dose is 240 mg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity.\textsuperscript{2} Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.\textsuperscript{2} Efficacy outcome measures included independent radiographic review committee- assessed confirmed ORR per RECIST 1.1, and duration of response.\textsuperscript{2} More than half of patients (51%) had a BRAF (16%) or KRAS (35%) mutation.\textsuperscript{1}

In this trial, Opdivo demonstrated an ORR of 28% (95% Cl: 17-42; 15/53) in patients who received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, including a 1.9% complete response rate (1/53) and a 26% partial response rate (14/53). Median duration of response in these patients was not reached (range: 2.8+–22.1+ months).\textsuperscript{2} Among all enrolled patients, 32% (95% Cl: 22-44; 24/74) responded to treatment with Opdivo, including a 2.7% complete response rate (2/74) and a 30% partial response rate (22/74). The median duration of response was not reached (range: 1.4+–26.5+ months).\textsuperscript{2} Data from CheckMate -142 were published in The Lancet Oncology in July.

“As the third most common type of cancer in the United States, our view is that colorectal cancer – particularly for those with dMMR or MSI-H metastatic disease – has been in need of new research and treatments.\textsuperscript{8} The approval of Opdivo for appropriate patients with this disease gives the community more hope,” said Michael Sapienza, chief executive officer of the Colon Cancer Alliance.

**Select Safety Profile**

The most common adverse reactions (≥20%) in patients who received Opdivo as a single agent were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia.\textsuperscript{2} Please see additional Important Safety Information below.

**About dMMR or MSI-H Colorectal Cancer**

Colorectal cancer (CRC) is cancer that develops in the colon or the rectum, which are part of the body's digestive or gastrointestinal system.\textsuperscript{9} In the United States, CRC is the third most common cancer, in 2017 it is estimated that there will be approximately 135,000 new cases of the disease and that it will be the second leading cause of cancer-related deaths among men and women combined.\textsuperscript{8,10} Approximately 5% of metastatic CRC patients have mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) tumors.\textsuperscript{3}

Mismatch repair deficiency occurs when the proteins that repair mismatch errors in DNA replication are missing or non-functional, which leads to MSI-H tumors in certain types of cancer, including CRC.\textsuperscript{5,11} Patients with dMMR or MSI-H metastatic CRC are less likely to benefit from conventional chemotherapy and typically have a poor prognosis.\textsuperscript{3,4,5} Routine testing to confirm dMMR or MSI-H status should be conducted for all metastatic CRC patients.\textsuperscript{7}

**INDICATION**

OPDVÒ\textsuperscript{®} (nivolumab) is indicated for the treatment of adults and pediatric (12 years and older) patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**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.

**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 for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. 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 hyperglycemia.

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

**Infusion Reactions**

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. 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 patients receiving OPDIVO monotherapy, infusion-related reactions occurred in 6.4% (127/1994) of patients.

**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.

**Common Adverse Reactions**

The most common adverse reactions (≥20%) in patients who received OPDIVO as a single agent were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia.²

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

**About the Opdivo Clinical Development Program**

Bristol-Myers Squibb’s global development program founded on scientific expertise in the field of Immuno-Oncology includes a broad range of clinical trials studying Opdivo, across all phases, including Phase 3, in a variety of tumor types. To date, the Opdivo clinical development program has enrolled more than 25,000 patients.

**About Bristol-Myers Squibb’s Patient Access Support**
Bristol-Myers Squibb remains committed to providing a comprehensive set of programs and services 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 Services 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 and co-pay assistance for eligible, commercially insured patients. More information about our access and reimbursement support services 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 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 and Facebook.

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, 2016 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


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