Bristol-Myers Squibb’s Opdivo® (nivolumab) Receives FDA Approval for the Treatment of Hepatocellular Carcinoma Patients Previously Treated with Sorafenib

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- **Opdivo is the first and only Immuno-Oncology agent to receive this FDA approval; this accelerated approval is based on tumor response rate and durability of response in these patients**
- **The CheckMate -040 pivotal study evaluated Opdivo in patients with and without active Hepatitis B or C infection, and across PD-L1 expression levels**
- **HCC is the most common type of liver cancer and incidence rates are increasing**

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 patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Approval for this indication has been granted under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

In the CheckMate -040 trial, 14.3%* (95% CI: 9.2-20.8; 22/154) of patients responded to treatment with Opdivo. The percentage of patients with a complete response was 1.9% (3/154) and the percentage of patients with a partial response was 12.3% (19/154). Among responders (n=22), responses ranged from 3.2 to 38.2+ months; 91% of those patients had responses of six months or longer and 55% had responses of 12 months or longer.

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 reactions; and embryo-fetal toxicity. Please see the Important Safety Information section below.

“We are proud to bring the potential for clinically meaningful responses with Immuno-Oncology therapy to these advanced-stage HCC patients, who have had limited treatment options for years,” said Chris Boerner, president, U.S. Commercial, Bristol-Myers Squibb. “Today’s approval marks an important step toward our mission of delivering transformational medicines to treat conditions with a high unmet need.”

The burden of liver cancer in the U.S. is significant and is expected to increase in the decades to come. A recently-released American Cancer Society (ACS) report published in CA: A Cancer Journal for Clinicians notes that death rates for liver cancer are increasing at a faster pace than any other cancer, doubling since the mid-1980s.

“Unfortunately, the majority of HCC patients are diagnosed with advanced-stage disease and are not candidates for potentially curative surgical interventions,” said Adrian M. Di Bisceglie, M.D., co-director, Saint Louis University Liver Center, Chief of Hepatology. “More options are needed for advanced-stage HCC patients who have failed prior systemic therapy.”

Hepatocellular carcinoma is often diagnosed in the advanced-stage where treatment options are limited and there is a high unmet need for patients who are intolerant to or who have progressed on sorafenib therapy.

“In recent years, there has been growing interest in leveraging immuno-oncology knowledge and discoveries to add to the treatment options available for patients with advanced-stage liver cancer,” said Anthony B. El-Khoueiry, M.D., lead investigator and associate professor of clinical medicine and phase I program director at the Keck School of Medicine of University of Southern California (USC) and the USC Norris Comprehensive Cancer Center. “The approval of Opdivo provides us with an encouraging approach and a new treatment option for appropriate patients with HCC following prior systemic
Approval Based on Notable Overall Response Rate and Duration of Response

CheckMate -040 included a Phase 1/2, open-label, multicenter study evaluating Opdivo in patients with HCC who progressed on or were intolerant to sorafenib. In this study, 154 patients received Opdivo 3 mg/kg administered intravenously every two weeks. The recommended dose is 240 milligrams administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity. Efficacy outcome measures included confirmed overall response rate (as assessed by blinded independent central review using RECIST v1.1 and modified RECIST for HCC) and duration of response. The median age of patients participating in the study was 63 (range: 19-81), all patients had received prior sorafenib therapy and 19% of patients had received two or more prior systemic therapies. Patients were enrolled regardless of PD-L1 expression level and whether or not they were infected with active Hepatitis B virus (HBV) or active Hepatitis C virus (HCV). Data from CheckMate -040 were presented at the American Society of Clinical Oncology 2017 Annual Meeting in June.

In the CheckMate -040 trial, 14.3% (95% CI: 9.2-20.8; 22/154) of patients responded to treatment with Opdivo. The percentage of patients with a complete response was 1.9% (3/154) and the percentage of patients with a partial response was 12.3% (19/154). Among responders (n=22), responses ranged from 3.2 to 38.2+ months; 91% of those patients had responses of six months or longer and 32% had responses of 12 months or longer. The median time to response was 2.8 months (range: 1.2-7.0). The overall response rate based on modified RECIST was 18.2% (95% CI: 12.4-25.2; 28/154). Complete response rate was 3.2% (5/154); partial response rate was 14.9% (23/154). Responses were observed across PD-L1 expression levels.

“I advocate for others because I know firsthand the terrible toll cancers of the liver take on a patient and their loved ones. In my opinion, HCC is an example of a cancer where awareness is out of sync with the impact of the disease,” said Suzanne Lindley, Co-Founder, Yes! Beat Liver Tumors. “Today’s approval shines a light of awareness and hope on a disease with a high unmet medical need.”

Select Safety Profile

The safety of Opdivo was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib in the CheckMate -040 study. Patients were required to have an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of no more than five times the upper limit of normal and total bilirubin of less than 3 mg/dL. The median duration of exposure to Opdivo was six months. Treatment with Opdivo resulted in treatment-emergent Grade 3 or 4 AST in 18% (27/154) of patients, Grade 3 or 4 ALT in 11% (16/154) of patients, and Grade 3 or 4 bilirubin in 7% (11/154) of patients. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients. Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia. The most common adverse reactions (≥20%) in patients receiving Opdivo (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). Opdivo was discontinued due to adverse reactions in 11% of patients and 32% of patients had a dose delay for an adverse reaction.

About Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the fastest-growing cause of cancer death in the U.S. It is estimated that there will be approximately 41,000 new cases of liver and intrahepatic bile duct cancer and 29,000 deaths from these diseases in the U.S. this year. The majority of these cases are caused by Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infections, making chronic infection with HBV or HCV the most common risk factor for liver cancer. However, the increasing prevalence of metabolic syndrome and nonalcoholic steatohepatitis (NASH) is expected to contribute to increased rates of HCC in the U.S. in the foreseeable future.

INDICATION

OPDIVO® (nivolumab) is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the 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. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3 and up to 5 times the upper limit of normal (ULN), if AST/ALT is >1 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients.

In Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.

**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 the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO, 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, facial edema, myalgia, polyarthritis, autoimmune myopathy, Guillain-Barré syndrome, hypophysitis, adenitis, hypophysitis, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), 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.

**Serious Adverse Reactions**

In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia.

**Common Adverse Reactions**

In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%).

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

**About the Opdivo Clinical Development Program**

Bristol-Myers Squibb’s global development program is founded on scientific expertise in the field of Immuno-Oncology and 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 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 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 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 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.

*BICR-assessed based on RECIST v1.1

**References**

9. Clinicaltrials.gov. “An Immuno-therapy Study to Evaluate the Effectiveness, Safety and Tolerability of Nivolumab or Nivolumab in Combination With Other Agents in Patients With Advanced Liver Cancer (CheckMate040). Available at: [https://clinicaltrials.gov/ct2/show/NCT01658878](https://clinicaltrials.gov/ct2/show/NCT01658878)

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**Ticker Slug:**
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*Exchange:* NYSE

#FDA approves new treatment option from $BMY for previously treated HCC, most common type of #LiverCancer