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Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration

[METASTATIC-MELANOMA-FACT-SHEET-11-25](#) →

First approval of Opdivo in the United States

Bristol-Myers Squibb Company (NYSE:BMJ) today announced that the U.S. Food and Drug Administration (FDA) approved *Opdivo* (nivolumab) injection, for intravenous use. *Opdivo* is a human programmed death receptor-1 (PD-1) blocking antibody indicated 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. 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. Metastatic melanoma is the deadliest form of skin cancer, and despite recent advances, there are limited treatment options available for patients who have been previously treated with approved agents.

This press release has an accompanying Smart Marketing Page providing further details about the organization, products and services introduced below. You can access the Smart Marketing Page via the following link: <https://smp.newshq.businesswire.com/pages/bristol-myers-squibb-receives-accelerated-approval-opdivo-nivolumab-us-food-and-drug-administr>.

"Bristol-Myers Squibb is pleased to be able to offer an important new option for patients who have progressed following treatment for unresectable or metastatic melanoma, which is one of the most aggressive forms of cancer," said **Lamberto Andreotti**, chief executive officer, Bristol-Myers Squibb. "The approval of *Opdivo*, the latest breakthrough medicine from our immuno-oncology pipeline, demonstrates our company's commitment to meeting the needs of these patients, and to leading advances in the science of immuno-oncology."

Opdivo is associated with immune-mediated: pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism and hyperthyroidism, other adverse reactions; and embryofetal toxicity. Please see the Important Safety Information section below.

The company expects to begin shipping *Opdivo* within one to two weeks of today's approval.

***Opdivo* Delivered A Response Rate of 32%**

Opdivo is the only PD-1 that has demonstrated efficacy in a Phase 3, pivotal clinical trial with advanced melanoma in patients who had been previously treated and progressed with *Yervoy* and, if BRAF mutation positive, a BRAF inhibitor. The efficacy of *Opdivo* was evaluated based on a single-

arm, non-comparative planned interim analysis of the first 120 patients who received *Opdivo* with a minimum of 6 months follow-up in the Phase 3 CheckMate -037 trial.

Opdivo achieved a 32% (95% CI: 23, 41) response rate (38/120) with a dosing strength and frequency of 3 mg/kg intravenously over 60 minutes every 2 weeks. 3% of patients (4/120) achieved a complete response, and 28% (34/120) achieved a partial response. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durability of response ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer. Responses to *Opdivo* were demonstrated in both patients with and without BRAF mutation.

The safety profile of *Opdivo* has been demonstrated in the pivotal, Phase 3 CheckMate-037 trial. 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. The most common adverse reaction (≥20%) reported with *Opdivo* was rash (21%). Please see the Important Safety Information section below.

"The approval of *Opdivo* gives patients and physicians an important new treatment option for a population where they were once very limited," said Jeffrey S. Weber, MD, Ph.D., director of the Donald A. Adam Comprehensive Melanoma Research Center at Moffitt Cancer Center. "For the first time, a PD-1 blocking antibody has shown a response rate of 32% in a Phase 3 randomized clinical trial of patients with unresectable or metastatic melanoma, who have progressed following first line therapy." Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received *Opdivo* in the CheckMate -037 trial in whom the minimum duration of follow up was 6 months.

"The emergence of effective immuno-oncology therapies that are capable of successfully treating metastatic melanoma has reinvigorated the field of cancer immunology with an optimism that immune based treatments will play a central role in therapeutic strategies for cancer patients," said Jill O'Donnell-Tormey, Ph.D., CEO and director of Scientific Affairs at the Cancer Research Institute, a nonprofit organization dedicated to advancing the science of cancer immunology.

About the CheckMate -037 Trial

CheckMate -037 was a randomized, Phase 3 trial evaluating *Opdivo* 3 mg/kg (n=268), administered every two weeks, or chemotherapy (n=102) (investigator's choice of either single-agent dacarbazine 1000 mg/m² every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m² every 3 weeks) in patients with advanced melanoma who had been previously treated and progressed with *Yervoy* and, if BRAF mutation positive, a BRAF inhibitor. No premedication is required with *Opdivo*.

The primary objective of this analysis of the CheckMate -037 trial was Objective Response Rate (ORR). CheckMate -037 included 90 participating trial sites in 14 countries, and included both institutional and community practice centers. The clinical study is ongoing to determine whether there is an overall survival benefit.

In the *Opdivo* treated patients (n=120), 76% of patients had M1C disease, 18% of patients had a history of brain metastases, and 56% of patients had elevated LDH levels. The median age of patients was 58. 22% of patients were BRAF V600 mutation positive.

Distinct Immune Pathway

Opdivo is approved for use in patients previously treated with *Yervoy*. Although both treatments are immunotherapies, PD-1 and CTLA-4 are distinct pathways.

About Bristol-Myers Squibb's Support Programs for *Opdivo*

As the leader in metastatic melanoma, Bristol-Myers Squibb remains committed to helping patients through treatment with *Opdivo*. For support and assistance, patients and physicians may call 1-855-OPDIVO-1. This number offers one-stop access to a range of support services for patients and healthcare professionals alike.

About Bristol-Myers Squibb's Access Support

Bristol-Myers Squibb is committed to helping patients access *Opdivo* and offers numerous programs to support patient and providers in gaining access. BMS Access Support[®], the Bristol-Myers Squibb Reimbursement Services program, is designed to support access to BMS medicines and expedite time to therapy through reimbursement support including Benefit Investigations, Prior Authorization Facilitation, Appeals Assistance, and assistance for patient out-of-pocket costs. BMS Access Support assists patients and providers throughout the treatment journey – whether it is at initial diagnosis or in support of transition from a clinical trial. More information about our reimbursement support services can be obtained by calling 1-800-861-0048 or by visiting www.bmsaccesssupport.com. For healthcare providers seeking *Opdivo* specific reimbursement information, please visit the BMS Access Support Product section by visiting www.bmsaccesssupportoncology.com.

About the *Opdivo* Clinical Development Program

Bristol-Myers Squibb has a broad, global development program to study *Opdivo* in multiple tumor types consisting of more than 50 trials – as monotherapy or in combination with other therapies – in which more than 7,000 patients have been enrolled worldwide.

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 574 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.9% (5/574) of patients receiving OPDIVO; no cases occurred in Trial 1. 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. 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. 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. 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. 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. 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, the following clinically significant, immune-mediated adverse reactions occurred in less than 1% of OPDIVO-treated patients: pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis. 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, Guillian-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

- 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.

Common Adverse Reactions

The most common adverse reaction (≥20%) reported with OPDIVO was rash (21%).

Please see [US Full Prescribing Information for OPDIVO](#).

About Metastatic Melanoma

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin. Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to the other organs, such as the lymph nodes, lungs, brain or other areas of the body. The incidence of melanoma has been increasing for at least 30 years. In 2014, an estimated 76,100 melanoma cases will be diagnosed in the U.S. Melanoma is mostly curable when treated in its early stages. However, in its late stages, the average survival rate is just 6 months with a 1-year survival of 25.5%, making it one of the most aggressive forms of cancer.

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 www.bms.com, or follow us on Twitter at <http://twitter.com/bmsnews>.

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Contact:

Media: Sarah Koenig, 609-252-4145 sarah.koenig@bms.com or Carrie

Fernandez, 609-419-5448 carrie.fernandez@bms.com or Christina

Trank, 609-419-5497 christina.trank@bms.com or Investors: John

Elicker, 609-252-4611 john.ellicker@bms.com or Ranya

Dajani, 609-252-5330 ranya.dajani@bms.com

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[BMS contacts](#)

Media inquiries:
media@bms.com

Investors relations:
investor.relations@bms.com

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