U.S. Food and Drug Administration Approves Opdivo® (nivolumab) as the First New Medication in Nearly 20 Years for Certain Patients with Previously Treated Small Cell Lung Cancer

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PRINCETON, N.J.

- **Opdivo is now the first Immuno-Oncology treatment approved for small cell lung cancer (SCLC) patients who received platinum-based chemotherapy and at least one other line of therapy**
- **Approval based on overall response rate and duration of response from the SCLC cohort of the Phase 1/2 CheckMate -032 trial**

**PRINCETON, N.J.--(BUSINESS WIRE)--) Bristol-Myers Squibb Company (NYSE:BMY) today announced that Opdivo (nivolumab) received approval from the U.S. Food and Drug Administration (FDA) as the first and only Immuno-Oncology treatment option for patients with metastatic small cell lung cancer (SCLC) whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy. Approval for this indication has been granted under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.**

“At Bristol-Myers Squibb, we recognize the critical need to provide patients with cancer therapies that may offer more durable responses – particularly for those living with hard-to-treat, aggressive diseases like small cell lung cancer,” said Sabine Maier, M.D., development lead, thoracic cancers, Bristol-Myers Squibb. “This approval builds on our heritage of bringing Immuno-Oncology therapies to patients with other types of thoracic cancers. It also reinforces our commitment to bringing transformative treatments to patients in urgent need of effective new options.”

**Opdivo** is associated with the following Warnings and Precautions: 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.

This approval for **Opdivo** in patients with SCLC whose cancer has progressed after two or more prior lines of therapy was granted priority review from the FDA.

The approval was based on data from the SCLC cohort of the ongoing Phase 1/2 CheckMate -032 study evaluating **Opdivo** in patients who experienced disease progression after platinum-based chemotherapy. Of 109 patients receiving **Opdivo** after platinum-based chemotherapy and at least one other prior line of therapy, 12% (n=13/109; 95% CI: 6.5-19.5) responded to treatment based on assessment by a Blinded Independent Central Review (BICR), regardless of PD-L1 expression. Twelve patients had a partial response (11%), and one patient had a complete response (0.9%). Among these responders, the median DOR was 17.9 months (95% CI: 7.9-42.1; range: 3.0-42.1 months). **Opdivo** was discontinued in 10% of patients, and one dose was withheld in 25% of patients for an adverse reaction. Serious adverse reactions occurred in 45% of patients. The approved dosing for **Opdivo** in this indication is 240 milligrams administered every 2 weeks by intravenous infusion until disease progression or unacceptable toxicity.

“While Immuno-Oncology innovations have dramatically changed how oncologists approach certain cancers, we have had limited progress for patients with small cell lung cancer,” said Leora Horn, M.D., M.Sc., associate professor of medicine, Ingram associate professor of cancer research, director of the thoracic oncology program and assistant vice chairman for faculty development, Vanderbilt University Medical Center. “Today’s approval of nivolumab is particularly exciting considering it is the first checkpoint inhibitor approved for these specific patients, and now we can finally treat this devastating disease from a different angle.”

Small cell lung cancer is one of two main types of lung cancer and accounts for about 10% to 15% of all lung cancers. Small
cell lung cancer is an aggressive disease, and symptoms often are not detected until the cancer is at an advanced stage. In the United States, about 27,000 cases of SCLC are expected to be diagnosed in 2018. From the time of diagnosis, five-year survival rates for extensive stage SCLC, or Stage IV, are about 2%. "Small cell lung cancer can be a very challenging disease, particularly for those who have already been through multiple types of treatment, as most patients relapse within a year of diagnosis," said Andrea Ferris, president and chairman of LUNGevity Foundation. "This approval marks a major milestone for the patients touched by this unrelenting disease and may motivate them to pursue further treatment where there previously were no other approved options."

Approval Based on CheckMate -032 Trial
CheckMate -032 is a Phase 1/2 multicenter, multi-cohort, open-label and ongoing trial, including 245 patients with SCLC who had experienced disease progression after platinum-based chemotherapy treated with Opdivo monotherapy. Efficacy was based on 109 patients who had experienced disease progression after platinum-based chemotherapy and at least one other prior line of therapy. These patients received 3 mg/kg of Opdivo given by intravenous infusion over 60 minutes every 2 weeks and were included regardless of their PD-L1 status. Infusions were administered to patients until disease progression or unacceptable toxicity. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable.

The first tumor assessments were conducted 6 weeks after the first dose and continued every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The major efficacy outcome measures were confirmed ORR, which was further characterized by DOR, as assessed by a BICR. The median duration of therapy in patients treated with Opdivo in the CheckMate -032 trial was 1 month (range: 0 to 44.2+ months). Seventeen percent of patients received Opdivo for greater than 6 months, and 9% of patients received Opdivo for greater than one year.

Select Safety Profile for the CheckMate -032 Trial
The safety was evaluated in 245 patients with SCLC who experienced disease progression after platinum-based chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, pneumonitis, pleural effusion and dehydration. The most common adverse reactions (reported in at least 20% of patients) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diarrhea (21%), constipation (20%) and cough (20%).

INDICATIONS
OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy. 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.

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.

OPDIVO® (nivolumab) is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

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 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 hypophysis, 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 hypophysis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysis. 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, hypophysis 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 3 or 4 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 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, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, 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 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 as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate study 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 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 -032, serious adverse reactions occurred in 45% of patients receiving OPDIVO (n=245). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, pneumonitis, pleural effusion, and dehydration. In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were
common adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis.

**Common Adverse Reactions**

In Checkmate 032, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=245) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diarrhea (21%), constipation (20%), and cough (20%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough and dyspnea at a higher incidence than investigator's choice.

**Checkmate Trials and Patient Populations**

Checkmate 032 – previously treated small cell lung cancer; Checkmate 017 – squamous non-small cell lung cancer (NSCLC); Checkmate 057 – non-squamous NSCLC; Checkmate 141 – squamous cell carcinoma of the head and neck.

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

**Bristol-Myers Squibb & Immuno-Oncology: Advancing Oncology Research**

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational medicines, including Immuno-Oncology (I-O) therapeutic approaches, for hard-to-treat cancers that could potentially improve outcomes for these patients.

We are leading the integrated scientific understanding of both tumor cell and immune system pathways, through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 50 types of cancers with 24 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance the I-O/I-O, I-O/chemotherapy, I-O/targeted therapies and I-O/radiation therapies across multiple tumors and potentially deliver the next wave of therapies with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and how a patient’s tumor biology can be used as a guide for treatment decisions throughout their journey.

We understand making the promise of transformational medicines like I-O therapies a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

**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 and 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 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 discussed in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2017 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.
References


Language:
English

Contact:
Bristol-Myers Squibb Company
Media Inquiries:
Laurel Sacks, 917-861-0746
laurel.sacks@bms.com
or
Investors:
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com

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#FDA approves $BMY therapy for certain previously treated patients with advanced small cell #LungCancer