CheckMate -025, a Pivotal Phase III Opdivo (nivolumab) Renal Cell Cancer Trial, Stopped Early

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Opdivo Demonstrates Superior Overall Survival Compared to Everolimus in Patients with Previously-Treated Advanced or Metastatic Renal Cell Carcinoma

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that an open-label, randomized Phase III study evaluating Opdivo (nivolumab) versus everolimus in previously-treated patients with advanced or metastatic renal cell carcinoma (RCC) was stopped early because an assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study met its endpoint, demonstrating superior overall survival in patients receiving Opdivo compared to the control arm. The company looks forward to sharing these data with health authorities soon.

“The results of CheckMate -025 mark the first time an Immuno-Oncology agent has demonstrated a survival advantage in advanced renal cell carcinoma, a patient group that currently has limited treatment options,” said Michael Giordano, senior vice president, Head of Development, Oncology, Bristol-Myers Squibb. “Through our Opdivo clinical development program, we aim to redefine treatment expectations for patients with advanced RCC by providing improved survival.”

CheckMate -025 investigators are being informed of the decision to stop the comparative portion of the trial. Bristol-Myers Squibb is working to ensure that eligible patients will be informed of the opportunity to continue or start treatment with Opdivo in an open-label extension as part of the company’s commitment to providing patient access to Opdivo, and characterizing long-term survival. The company will complete a full evaluation of the final CheckMate -025 data and work with investigators on the future presentation and publication of the results.

About CheckMate -025

CheckMate -025 is a Phase III, open-label, randomized study of Opdivo versus everolimus in previously-treated patients with advanced or metastatic clear-cell renal cell carcinoma. The trial randomized 821 patients to receive either nivolumab 3 mg/kg intravenously every two weeks or everolimus 10 mg tablets by mouth daily until documented disease progression or unacceptable toxicity. The primary endpoint is overall survival. Secondary endpoints include objective response rate and progression-free survival.

About Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults, accounting for more than 100,000 deaths worldwide each year. Clear-cell RCC is the most prevalent type of RCC and constitutes 80 percent to 90 percent of all cases. RCC is approximately twice as common in men as in women, with the highest rates of the disease in North America and Europe. Globally, the five-year survival rate for those diagnosed with metastatic, or advanced kidney cancer, is 12.1 percent.

Immuno-Oncology at Bristol-Myers Squibb

Surgery, radiation, cytotoxic or targeted therapies have represented the mainstay of cancer treatment over the last several decades, but long-term survival and a positive quality of life have remained elusive for many patients with advanced disease.

To address this unmet medical need, Bristol-Myers Squibb is leading research in an innovative field of cancer research and treatment known as Immuno-Oncology, which involves agents whose primary mechanism is to work directly with the body’s immune system to fight cancer. The company is exploring a variety of compounds and immunotherapeutic approaches for patients with different types of cancer, including researching the potential of combining Immuno-Oncology agents that target different pathways in the treatment of cancer.

Bristol-Myers Squibb is committed to advancing the science of Immuno-Oncology, with the goal of changing survival expectations and the way patients live with cancer.

About Opdivo

Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that has received approval from the U.S. Food and Drug Administration (FDA) as a monotherapy in two cancer indications. On March 4, 2015, Opdivo received FDA approval for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-
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.

Other Immune-Mediated Adverse Reactions

- In Trial 1 and 3 (n=385), the following clinically significant immune-mediated adverse reactions occurred in <2% of OPDIVO-treated patients: adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis. 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, Guillain-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.

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 none of the 102 patients receiving chemotherapy. In Trial 3, hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. Hyperthyroidism occurred in 1.7% (2/117) of patients receiving OPDIVO; no cases occurred in Trial 1 or Trial 3. In Trial 1, hypothyroidism, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated hypothyroidism occurred in 2.2% (6/268) of patients receiving OPDIVO; one with Grade 3 and five with Grade 2. In Trial 3, immune-mediated hypothyroidism occurred in 6% (7/117) of patients receiving OPDIVO, including, five Grade 3 and two Grade 2 cases. Monitor patients for signs and symptoms of hypothyroidism. Administer corticosteroids for Grade 2 or greater hypothyroidism. 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. In Trial 3, diarrhea occurred in 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated colitis occurred in 9.9% (1/117) of patients. 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. In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). 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. In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) 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 Pneumonitis

- In the U.S., Opdivo is also 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. Opdivo became the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world on July 4, 2014 when Ono Pharmaceutical Co. announced that it received manufacturing and marketing approval in Japan for the treatment of patients with unresectable melanoma. 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 8,000 patients have been enrolled worldwide.

Immune-Mediated Hepatitis

- In Trial 1, 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated hypothyroidism occurred in 2.2% (6/268) of patients receiving OPDIVO; five with Grade 3 and one with Grade 2. In Trial 3, 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated hypothyroidism occurred in 9.9% (1/117) of patients. Monitor patients for immune-mediated hypothyroidism. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 hypothyroidism. Withhold OPDIVO for Grade 2 or 3. Permanently discontinue OPDIVO for Grade 4 hypothyroidism or recurrent hypothyroidism upon restarting OPDIVO.

Immune-Mediated Colitis

- In Trial 1, diarrhea 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. In Trial 3, diarrhea occurred in 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated colitis occurred in 9.9% (1/117) of patients. 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. In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). 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. In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) 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, 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Grade 1 or 2 hypothyroidism occurred in 3% (8/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. In Trial 3, hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. Hyperthyroidism occurred in 1.7% (2/117) of patients, including one Grade 2 case. Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism.
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

- In Trial 1, 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.
- In Trial 3, serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse drug reactions reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemothysis, and pain.

Common Adverse Reactions

- The most common adverse reactions (≥20%) reported with OPDIVO in Trial 1 were rash (21%) and in Trial 3 were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%).

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

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, Bristol-Myers Squibb and Ono Pharmaceutical 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 www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

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. Among other risks, there can be no guarantee that Opdivo will receive regulatory approval for an additional indication in RCC. 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, 2014 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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