Bristol-Myers Squibb to Present New Data Advancing Research Across Serious Liver Diseases at The Liver Meeting® 2017

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New analyses from a Phase 2 study of BMS-986036 (pegylated FGF21) in NASH further support non-invasive methods for assessing liver fibrosis

New analyses from CheckMate -040 demonstrating efficacy and safety of Opdivo in patients with HCC, including those infected with chronic HBV or HCV, to be featured in a Presidential Plenary

PRINCETON, N.J. -- (BUSINESS WIRE) -- Bristol-Myers Squibb Company (NYSE:BMY) today announced that new data across serious liver diseases, including nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC), will be presented at The Liver Meeting® 2017 in Washington, DC, October 20 – 24, 2017.

Key data presentations include:

- Two analyses from a Phase 2 study of BMS-986036 (pegylated FGF21) in NASH, which provide further support of non-invasive methods, including imaging studies and serum Pro-C3, for assessing liver fibrosis
- Updated data for Opdivo (nivolumab) in HCC from CheckMate -040, the trial which was the basis for the recent FDA approval for the treatment of HCC patients previously treated with sorafenib, will be presented in a Presidential Plenary

“The data being presented at The Liver Meeting® demonstrate our commitment to advancing the science in HCC and NASH, two serious liver diseases with unmet medical need,” said Tom Lynch, M.D., executive vice president and chief scientific officer, Bristol-Myers Squibb. “We are excited to share new analyses for Opdivo in HCC from CheckMate -040. In NASH, the breadth of the data that we and our collaborators are presenting reinforces our focus on investigating new treatment options for liver fibrosis and improving diagnostic processes, and these results are shaping the development program for BMS-986036.”

The Company is engaged in productive discussions with health authorities to advance the development program for BMS-986036.

Bristol-Myers Squibb exclusively licensed the rights to research, develop and commercialize BMS-986036 from Ambrx, Inc.

Also at The Liver Meeting®, Nitto Denko will present the results of a Phase 1b/2 study of HSP47 (ND-L02-s0201), which was licensed by Bristol-Myers Squibb for investigation in advanced liver fibrosis. Nordic Bioscience, with which Bristol-Myers Squibb collaborates to research collagen biomarkers in liver fibrosis, will share new data on Pro-C3, a biomarker that specifically detects the formation of type III collagen and can be measured with a blood test. Validated biomarkers are needed to assess disease activity and response to interventions in patients with NASH.

Bristol-Myers Squibb will also present study results regarding the occurrence of Hepatitis B Virus (HBV)-associated and other clinical and treatment-associated outcome events in patients taking long-term Baraclude vs. other nucleos(t)ide monotherapy. Bristol-Myers Squibb research tied to Hepatitis B and C during the past two decades has played a transformational role in the treatment of viral hepatitis around the globe.

Bristol-Myers Squibb data presentations at The Liver Meeting® 2017:

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Nivolumab in Sorafenib-Naive and -Experienced Patients with Advanced Hepatocellular Carcinoma: Survival, Hepatic Safety, and Biomarker Assessments in CheckMate 040

B. Sangro / Presidential Plenary Oral Oct. 23, 2017 8:30 – 8:45 a.m. Presidential Plenary: Clinical Convention Center Ballroom

Treatment Patterns and Healthcare (HC) Costs by Lines of Therapy Among Advanced Hepatocellular Carcinoma (aHCC) Patients Treated with Systemic Cancer Therapy

M. Bonafede / Poster Oct. 22, 2017 12:30 – 2:00 p.m. Clinical Liver Cancer Hall D

Prospective, Randomized Assessment of HBV-associated and other Clinical Outcome Events During Long-Term Therapy With Entecavir or Other HBV Nucleos(t)ide Analogues in Patients with Chronic HBV Infection

J. Hou / Oral Oct. 22, 2017 8:45 – 9:00 a.m. Parallel 3: Hepatitis B: Approved Treatments Room 207

BMS-986036 (pegylated FGF21) in Patients with Non-Alcoholic Steatohepatitis: A Phase 2 study


Multi-Biomarker Validation of MRI-PDFF- and MRE-Derived Treatment Response with BMS-986036 (peg-FGF21): A Secondary Analysis of a Multi-center Clinical Trial in Non-Alcoholic Steatohepatitis (NASH).

R. Loomba / Poster Oct. 20, 2017 12:00 – 1:30 p.m. Imaging and Noninvasive Fibrosis Assessment Hall D

Baseline Serum Pro-C3 Predicts Response to BMS-986036 (peg-FGF21): A Secondary Analysis of a Multi-Center Clinical Trial in Non-Alcoholic Steatohepatitis (NASH)

M. Abdelmalek / Poster Oct. 23, 2017 12:30 – 2:00 p.m. Steatosis and Steatohepatitis Hall D

Bristol-Myers Squibb collaborator presentations include:

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<td>Development and Validation of the Collagen Neo-Epitope Biomarker Pro-C3 “FIB-C3 Score” for Detection and Staging of Advanced Non-Alcoholic Fatty Liver Disease in a Large International Multi-Centre Patient Cohort</td>
<td>M. Boyle / Oral</td>
<td>Oct. 22, 2017 3:00 – 3:45 p.m.</td>
<td>Parallel 14: Novel Biomarkers for NASH Room 202</td>
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<td>Insulin secretion and decreased glucose clearance are associated with enhanced fibrogenesis and a high risk of disease progression in non-diabetic patients with Non Alcoholic Fatty Liver Disease.</td>
<td>R. Younes / Poster</td>
<td>Oct. 23, 2017 12:30 p.m. – 2:00 p.m.</td>
<td>Steatosis and Steatohepatitis Hall D</td>
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<td>The Extracellular Matrix (ECM) Turnover Profile in Cholestatic and Autoimmune Liver Diseases – an Exploratory Study.</td>
<td>M. Nielsen / Poster</td>
<td>Oct. 20, 2017 12:00 – 1:30 p.m.</td>
<td>Autoimmune and Cholestatic Liver Disease Hall D</td>
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<td>Treatment with ND-L02-s0201, a Novel Targeted Lipid Nanoparticle (LNP) Delivering HSP47 siRNA, Results in Fibrosis Resolution in Preclinical Rat Models</td>
<td>Y. Liu/Poster</td>
<td>Oct. 20, 2017 12:00 – 1:30 p.m.</td>
<td>Clinical Research and Translational Fibrosis Research Hall D</td>
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<td>Clinical Phase 1b/2 Study Results for Safety, Pharmacokinetics, and Efficacy of ND-L02-s0201, a Novel Targeted lipid Nanoparticle (LNP) Delivering HSP47 siRNA for the Treatment of Patients with Advanced Liver Fibrosis</td>
<td>E. Lawitz/Poster</td>
<td>Oct. 20, 2017 12:00 – 1:30 p.m.</td>
<td>Clinical and Translational Fibrosis Research Hall D</td>
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About Fibrosis and NASH

Fibrotic diseases are characterized by chronic inflammation that leads to excess collagen deposition and scar formation in an organ or tissue. This scarring response compromises function and can ultimately lead to organ failure. Nonalcoholic steatohepatitis (NASH) may progress to cirrhosis, hepatocellular carcinoma (HCC), the most common type of liver cancer, and liver failure, and is expected to be the leading cause of liver transplantation by 2020. The severity of liver fibrosis (scar tissue in the liver) is measured on a scale of F0 (normal) to F4 (cirrhosis) in a liver biopsy specimen. Approximately 20 million patients in the U.S. have NASH, and there are currently no approved pharmacological treatments.

About Fibrosis at Bristol-Myers Squibb
Bristol-Myers Squibb is committed to the discovery and development of medicines for the treatment of fibrosis, the buildup of scar tissue that impacts organ function. We are advancing a robust pipeline of investigational compounds to address areas of high unmet need in patients with fibrotic diseases, including nonalcoholic steatohepatitis (NASH), a condition with no approved pharmacological treatment options that may lead to liver fibrosis and/or cirrhosis; and idiopathic pulmonary fibrosis (IPF), a progressive lung disease with a high mortality rate. We are researching multiple mechanisms and approaches to make the biggest impact on patients.

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. More than 700,000 people around the world, including about 41,000 people in the U.S., are diagnosed with HCC each year. The majority of these cases are caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, making HBV/HCV the most common risk factors for liver cancer. In the foreseeable future, the rising prevalence of metabolic syndrome and nonalcoholic steatohepatitis (NASH) is expected to contribute to increased rates of HCC.

HCC is often diagnosed in the advanced stage where treatment options have been limited and outcomes poor, with one-year survival rates in the advanced setting of approximately 44%. The FDA recently approved Opdivo® for the treatment of HCC following prior systemic therapy based on tumor response rate and durability of response, offering an additional treatment option to appropriate patients.

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 Immuno-Oncology (I-O) medicines for hard-to-treat cancers that could potentially improve outcomes for these patients.

We are leading the scientific understanding of I-O 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 14 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance 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 patients' individual tumor biology can be used as a guide for treatment decisions throughout their journey.

We understand making the promise of I-O 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 Opdivo
Opdivo® is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response. By harnessing the body's own immune system to fight cancer, Opdivo® has become an important treatment option across multiple cancers.

Opdivo®'s leading global development program is based on Bristol-Myers Squibb's scientific expertise in the field of Immuno-Oncology and includes a broad range of clinical trials 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. The Opdivo® trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from Opdivo® across the continuum of PD-L1 expression.

In July 2014, Opdivo® was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. Opdivo® is currently approved in more than 60 countries, including the United States, the European Union and Japan. In October 2015, the company's Opdivo® and Yervoy® combination regimen was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 50 countries, including the United States and the European Union.

U.S. FDA-APPROVED INDICATIONS FOR OPDIVO®

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with Yervoy® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the 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 advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has
relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. 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 recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

OPDIVO ® (nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor 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 adult 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 the confirmatory trials.

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

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

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. In patients receiving OPDIVO with YERVOY, immune-mediated pneumonitis occurred in 6% (25/407) of patients.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=12).

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. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that study (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

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 without HCC, withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. 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 patients receiving OPDIVO with YERVOY, immune-mediated hepatitis occurred in 13% (51/407) of patients.
In Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%.

**Immune-Mediated Neuropathies**

In a separate Phase 3 study of YERVOY 3 mg/kg, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.

**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 6.6% (12/1994) of patients. In patients receiving OPDIVO with YERVOY, hypophysitis occurred in 9% (36/407) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO with YERVOY, adrenal insufficiency occurred in 5% (21/407) 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 with YERVOY, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (88/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with YERVOY. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO with YERVOY, diabetes occurred in 1.5% (6/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. 6 of the 9 patients were hospitalized for severe endocrinopathies.

**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. In patients receiving OPDIVO with YERVOY, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients.

**Immune-Mediated Skin Adverse Reactions and Dermatitis**

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. In patients receiving OPDIVO with YERVOY, immune-mediated rash occurred in 22.6% (92/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 (2.5%) patients. 1 (0.2%) patient died as a result of toxic epidermal necrolysis. 1 additional patient required hospitalization for severe dermatitis.

**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 one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one patient receiving OPDIVO with YERVOY (0.2%) after 1.7 months of exposure.

**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 monotherapy or in combination with YERVOY, 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, 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. In patients receiving OPDIVO with YERVOY, infusion-related reactions occurred in 2.5% (10/407) of patients.

Complications of Allogeneic HSCT after OPDIVO
Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Embryo-Fetal Toxicity
Based on their mechanisms of action, OPDIVO and YERVOY 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- or YERVOY-containing regimen and for at least 5 months after the last dose of OPDIVO.

Lactation
It is not known whether OPDIVO or YERVOY 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. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

Serious Adverse Reactions
In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). 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 Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). 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 at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. 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 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) were dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (59%), rash (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common (≥20%) adverse reactions in the OPDIVO (n=313) arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 017 and 057, the most common adverse reactions were rash (21%), pyrexia (13%), and diarrhea (13%). In Checkmate 066, the most common adverse reactions were fatigue (39%), musculoskeletal pain (32%), rash (28%), pruritus (23%), and vomiting (28%).
common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were asthenic conditions (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO were cough and dyspnea at a higher incidence than investigator’s choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). 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%). 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, and pyrexia.

In a separate Phase 3 study of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

**Checkmate Trials and Patient Populations**

- **Checkmate 067** – advanced melanoma alone or in combination with YERVOY; **Checkmate 037 and 066** – advanced melanoma; **Checkmate 017** – squamous non-small cell lung cancer (NSCLC); **Checkmate 057** – non-squamous NSCLC; **Checkmate 025** – renal cell carcinoma; **Checkmate 205/039** – classical Hodgkin lymphoma; **Checkmate 141** – squamous cell carcinoma of the head and neck; **Checkmate 275** – urothelial carcinoma; **Checkmate 040** – hepatocellular carcinoma.

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY.

**U.S. Indication and Important Safety Information - BARACLUDE® (entecavir):**

**INDICATION**

BARACLUDE (entecavir) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults and pediatric patients 2 years of age or older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The following points should be considered when initiating therapy with BARACLUDE:

- In adult patients, this indication is based on clinical trial data in nucleoside-inhibitor treatment-naïve and lamivudine-resistant subjects with HBeAg-positive and HBeAg-negative HBV infection and compensated liver disease and a more limited number of subjects with decompensated liver disease.

- In pediatric patients 2 years of age and older, this indication is based on clinical trial data in nucleoside-inhibitor-treatment-naïve and in a limited number of lamivudine experienced subjects with HBeAg-positive chronic HBV infection and compensated liver disease.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, AND LACTIC ACIDOSIS AND HEPATOMEGALY**

- Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

- Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if BARACLUDE is used to treat chronic HBV infection in patients with HIV infection that is not being treated. Therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART).

- Lactic acidosis and severe hepaticomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, alone or in combination with antiretrovirals.

**Warnings and Precautions**

- Before initiating BARACLUDE therapy, HIV antibody testing should be offered to all patients. BARACLUDE has not been studied as a treatment for HIV infection and is not recommended for this use.

- Lactic acidosis with BARACLUDE use has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures. Patients with decompensated liver disease may be at higher risk for lactic acidosis. BARACLUDE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

**Adverse Reactions**

- In clinical trials in patients with compensated liver disease, the most common (≥3%) adverse reactions of any severity with at least a possible relation to study drug for BARACLUDE-treated subjects were headache, fatigue, dizziness, and
In these trials, the most common adverse reactions of moderate to severe intensity (grades 2-4) were: diarrhea, dyspepsia, nausea, vomiting, fatigue, headache, dizziness, somnolence, and insomnia.

- In the decompensated liver disease trial, the most common adverse reactions of any severity among patients treated with BARACLUDE, regardless of causality, included: peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). In this trial, 18% (18/102) of BARACLUDE patients and 20% (18/89) of adefovir patients died during the first 48 weeks of therapy. The majority of those deaths were due to liver-related causes.

**Drug Interactions**

- BARACLUDE (entecavir) is primarily eliminated by the kidneys; therefore coadministration of BARACLUDE with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Patients should be monitored closely when receiving BARACLUDE with other renally-eliminated drugs.

**Pregnancy and Nursing Mothers**

- There are no adequate and well-controlled studies of BARACLUDE in pregnant women. BARACLUDE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- There are no studies on the effect of BARACLUDE on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.
- It is not known whether BARACLUDE is excreted into human milk; however, many drugs are excreted into breast milk. Due to the potential for serious adverse reactions in nursing infants from BARACLUDE, risks and benefits should be considered when deciding whether to discontinue breast-feeding or discontinue BARACLUDE in nursing women.

**Pediatric Use**

- The adverse reactions observed in pediatric patients who received treatment with BARACLUDE were consistent with those observed in clinical trials of BARACLUDE in adults. Adverse drug reactions reported in greater than 1% of pediatric patients included abdominal pain, rash events, poor palatability (“product taste abnormal”), nausea, diarrhea, and vomiting.
- Due to limited data, in lamivudine-experienced pediatric patients, Baraclude should be used only if the potential benefit justifies the potential risk to the child. Consideration should be given to the impact of BARACLUDE on future treatment options.

**Renal Impairment**

- Dosage adjustment of BARACLUDE is recommended for patients with a creatinine clearance <50 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis. There is insufficient data to recommend specific dosage adjustments of BARACLUDE in pediatric patients with renal impairment, however dosage adjustments similar to those for adults should be considered.

**Liver Transplant Recipients**

Liver function must be carefully monitored both before and during treatment with BARACLUDE in a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus.

**Duration of Therapy**

- The optimal duration of treatment with BARACLUDE for patients with chronic HBV infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

**Additional Information**

BARACLUDE is not a cure for HBV. Patients should be advised that treatment with BARACLUDE has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

**Please click here for the BARACLUDE full prescribing information, including Boxed WARNINGS.**

**About the Bristol-Myers Squibb and Ono Pharmaceutical Co., Ltd. Collaboration**

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Ltd. (Ono), 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 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. Among other risks, there can be no guarantee that any of the compounds or products mentioned in this release will receive regulatory approval for any of the indications described.
herein. 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.

Language:
English

Contact:
Bristol-Myers Squibb
Media:
Chrissy Trank, 609-252-5609
Christina.trank@bms.com
or
Audrey Abermathy, 919-605-4521
audrey.abemathy@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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