U.S. Food and Drug Administration Approves Opdivo® (nivolumab) + Yervoy® (ipilimumab) for Patients with Hepatocellular Carcinoma (HCC) Previously Treated with Sorafenib

**Release Date:**
Wednesday, March 11, 2020 6:59 am EDT

**Terms:**
Corporate/Financial News  $BMY  BMS  Bristol Myers  Squibb

**Dateline City:**
PRINCETON, N.J.

**Opdivo + Yervoy is the first and only dual immunotherapy approved in this setting**

Approval based on CheckMate -040 trial in which Opdivo + Yervoy showed an overall response rate of 33% (16/49; 95% CI: 20-48) in this patient population

**Opdivo + Yervoy combination is now approved to treat four types of cancer**

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol Myers Squibb Company (NYSE: BMY) today announced that Opdivo (nivolumab) 1 mg/kg plus Yervoy (ipilimumab) 3 mg/kg (injections for intravenous use) was approved by the U.S. Food and Drug Administration (FDA) to treat hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib. Approval for this indication has been granted under accelerated approval based on overall response rate and duration of response seen in the Opdivo + Yervoy cohort of the Phase 1/2 CheckMate -040 trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

“HCC is an aggressive disease in need of different treatment approaches,” said Anthony B. El-Khoueiry, M.D., lead investigator and associate professor of clinical medicine and phase I program director at the Keck School of Medicine, University of Southern California (USC) and the USC Norris Comprehensive Cancer Center. “The overall response rate observed in the Opdivo + Yervoy cohort of the CheckMate -040 trial underscores the potential of this dual immunotherapy as a possible treatment option for patients.”

In the CheckMate -040 cohort of HCC patients previously treated with sorafenib, after a minimum follow up of 28 months, 33% (16/49; 95% CI: 20-48) of patients responded to treatment with Opdivo + Yervoy; 8% (4/49) had a complete response (CR) and 24% (12/49) had a partial response (PR). Duration of responses (DOR) ranged from 4.6 to 30.5+ months, with 88% lasting at least six months, 56% at least 12 months and 31% at least 24 months. Overall response rate (ORR) and DOR were assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). ORR assessed by BICR using modified RECIST was 35% (17/49; 95% CI: 22-50), with a CR reported in 12% (6/49) of patients and a PR reported in 22% (11/49) of patients.

Opdivo is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when Opdivo is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials. Please see the Important Safety Information section below, including Boxed WARNING for Yervoy (ipilimumab) regarding immune-mediated adverse reactions, as well as select safety information from CheckMate -040.

“The incidence of liver cancer is rising in the United States, and HCC is the most common and aggressive form of the disease,” said Andrea Wilson, president and founder, Blue Faery: The Adrienne Wilson Liver Cancer Association. “Today’s approval provides a new option for patients with HCC previously treated with sorafenib, giving the community more hope.”
Opdivo + Yervoy is the only dual immunotherapy approved by the FDA in this setting. The therapy features a potentially synergistic mechanism of action that targets two different checkpoints (PD-1 and CTLA-4) and works in complementary ways.\(^1\)

“We recognize there is a critical need to provide patients with aggressive forms of cancer, like HCC, new treatment options that may offer clinically meaningful and ultimately durable responses,” said Adam Lenkowsky, general manager and head, U.S., Oncology, Immunology, Cardiovascular, Bristol Myers Squibb. “Today’s announcement builds on our legacy in pioneering immunotherapy treatments and is an important step in our commitment to transforming patients’ lives through science.”

Opdivo + Yervoy was granted Breakthrough Therapy Designation for this indication and a Priority Review from the FDA.

*Dr. Anthony B. El-Khoueiry is a paid consultant for Bristol Myers Squibb.

About the CheckMate -040 Trial Design
CheckMate -040 (NCT01658878) is a Phase 1/2 open-label study that included a cohort of patients with HCC who progressed on or were intolerant to sorafenib and received Opdivo + Yervoy.\(^1,10\) The trial included patients who were PD-L1 expressors and non-expressors.\(^2\) Key eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis status.\(^1\) Additional eligibility criteria included those who were infected with active HCV or active HBV, or were uninfected.\(^1,3\) Patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with HBV and HCV or HBV and HDV were excluded.\(^4\) Patients with known fibrolamellar HCC, sarcomatoid HCC, and mixed cholangiocarcinoma and HCC were also excluded.\(^5\) A total of 49 patients were treated with Opdivo 1 mg/kg IV and Yervoy 3 mg/kg IV every three weeks for four doses, followed by Opdivo 240 mg every two weeks until disease progression or unacceptable toxicity.\(^6\) The major efficacy outcome was ORR, as assessed by BICR using RECIST v1.1 and mRECIST.\(^1\) Duration of response was also assessed.\(^1\)

Select Safety Profile from CheckMate -040 Study
The safety of Opdivo 1 mg/kg and Yervoy 3 mg/kg was evaluated in 49 patients.\(^1\) Serious adverse reactions occurred in 59% of patients receiving Opdivo + Yervoy.\(^1\) Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.\(^1\) Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.\(^1\) The most common adverse reactions (reported in ≥20% of patients) were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%).\(^1\)

Indications
OPDVO\(^\text{®}\) (nivolumab), in combination with YERVOY\(^\text{®}\) (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma.

OPDVO\(^\text{®}\) (nivolumab), in combination with YERVOY\(^\text{®}\) (ipilimumab), is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

OPDVO\(^\text{®}\) (nivolumab), in combination with YERVOY\(^\text{®}\) (ipilimumab), is indicated for the treatment of adults and pediatric patients 12 years and older 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 confirmatory trials.

OPDVO\(^\text{®}\) (nivolumab), in combination with YERVOY\(^\text{®}\) (ipilimumab), 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 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.

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

OPDVO 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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) 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. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 10% (5/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 7% (8/119) of patients.

In a separate Phase 3 trial 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 trial (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 increases to >10 times ULN at baseline and increases to >5 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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 13% (51/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 20% (10/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 8% (10/119) of patients.

In a separate Phase 3 trial 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 trial 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, and hyperglycemia. Monitor thyroid function periodically during treatment, and hypertension. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 9% (36/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 4% (2/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hypophysitis occurred in 3.4% (4/119) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 5% (21/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 18% (9/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (41/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 5.9% (7/119) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hyperthyroidism occurred in 9% (171/1994)
of patients. Hypothyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hypothyroidism occurred in 8% (34/407) of patients receiving this dose of OPDIVO with YERVOY. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients. Hypothyroidism occurred in 10% (54/497) of patients receiving this dose of OPDIVO with YERVOY. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients. Hypothyroidism occurred in 12% (66/547) of patients receiving this dose of OPDIVO with YERVOY. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 15% (18/119) of patients. Hypothyroidism occurred in 12% (14/119) of patients. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, diabetes occurred in 1.5% (6/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) of patients.

In a separate Phase 3 trial 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. Six 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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 3 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 1.7% (2/119) 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 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 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 melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 22.6% (92/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 35% (17/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16% (90/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 14% (17/119) of patients.

In a separate Phase 3 trial 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. An 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 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. Encephalitis occurred in one melanoma patient receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, and immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 1.7% (2/119) of patients.

**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 neuropsychiatric, 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-Related Reactions**

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related 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 trial 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. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients.

**Embryo-Fetal Toxicity**

Based on mechanism 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 OPDIVO or YERVOY and for at least 5 months after the last dose.

**Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone**

In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**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 OPDIVO or YERVOY, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

**Serious Adverse Reactions**

In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%), or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) 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 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, hypophysitis, rash, dizziness (20%), neurotoxicity, asthenia, pyrexia, anemia, and leukopenia (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diabetes, hematologic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

**Common Adverse Reactions**

In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY (n=49) were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decrease (20%).

In a separate Phase 3 trial 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%).

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

**Bristol Myers Squibb: Advancing Oncology Research**

At Bristol Myers Squibb, patients are at the center of everything we do. The focus of our research is to increase quality, long-term survival for patients and make cure a possibility. Through a unique multidisciplinary approach powered by translational science, we harness our deep scientific experience in oncology and Immuno-Oncology (I-O) research to identify novel treatments tailored to individual patient needs. Our researchers are developing a diverse, purposefully built pipeline designed to target different immune-system pathways and address the complex and specific interactions between the tumor, its microenvironment and the immune system. We source innovation internally, and in collaboration with academia, government, advocacy groups and biotechnology companies, to help make the promise of transformational medicines, like I-O, a reality for patients.
About Bristol Myers Squibb’s Patient Access Support

Bristol Myers Squibb remains committed to providing assistance so that cancer patients who need our medicines can access them and expedite 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, as well as 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, Opdivo 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, Facebook and Instagram.

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

Cautionary Statement Regarding Forward-Looking Statements

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that continued approval of Opdivo in combination with Yervoy for the additional indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials, that future study results will be consistent with the results to date, and whether Opdivo in combination with Yervoy for such additional indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb’s business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

References

#FDA approves new $BMY therapy for patients with previously treated hepatocellular carcinoma