Bristol-Myers Squibb Receives FDA Approval for Opdivo (nivolumab) as Adjuvant Therapy in Patients with Completely Resected Melanoma with Lymph Node Involvement or Metastatic Disease

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Opdivo, the first and only anti-PD-1 immune checkpoint inhibitor approved for adjuvant treatment of melanoma, is indicated for both BRAF mutant and wild type patients

In the Phase 3 CheckMate -238 clinical trial, Opdivo 3 mg/kg demonstrated unprecedented recurrence-free survival versus Yervoy (ipilimumab) 10 mg/kg and was well tolerated 1,2

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) injection for intravenous use for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.1 The purpose of adjuvant therapy is to reduce the risk of recurrence following surgical removal of the tumor and lymph nodes that contain cancer. In the Phase 3 CheckMate -238 trial, Opdivo significantly improved recurrence-free survival (RFS) versus an active comparator, Yervoy (ipilimumab), in patients with stage IIIIB/C or stage IV melanoma after surgery.1,2 This benefit was observed across important subgroups, including in both BRAF mutant and BRAF wild-type patients.1 Opdivo is the first and only agent approved for the adjuvant treatment of melanoma based on a head-to-head trial against an active comparator with a proven overall survival benefit.1-3

“Today’s approval builds on our leadership in melanoma, offering physicians a new option with the potential to change the course of the disease through earlier intervention. Opdivo is the first PD-1 inhibitor approved as an adjuvant treatment for any cancer,” said Johanna Mercier, head, U.S. Commercial, Bristol-Myers Squibb. “Our decision to study Opdivo versus Yervoy – an established standard of care with a proven survival benefit – represents our relentless pursuit to bring more effective treatments to patients.”

In the CheckMate -238 clinical trial, Opdivo demonstrated an 18-month RFS rate of 66.4% [95% confidence interval (CI): 61.8 to 70.6] compared with 52.7% for Yervoy (95% CI: 47.8 to 57.4), with the median RFS not yet reached in either group. Opdivo reduced the risk of disease recurrence by 35% versus Yervoy [hazard ratio (HR): 0.65; 95% CI: 0.53 to 0.80; p <0.0001].1,2

Opdivo is associated with the following Warnings and Precautions: immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion reactions; and embryo-fetal toxicity. Please see the Important Safety Information section below, including Boxed WARNING for Yervoy regarding immune-mediated adverse reactions, as well as additional information on the CA 184-029 trial.1,3

Opdivo received Breakthrough Therapy Designation from the FDA for the adjuvant treatment of patients with high-risk, fully resected melanoma in September 2017. Approximately three in every 10 patients with stage III melanoma currently receive adjuvant therapy after surgery.4 Even with available treatment options, the majority of stage IIIIB and IIIIC melanoma patients (71% and 85%, respectively) experience disease recurrence within five years.5

Opdivo is the first programmed death-1 (PD-1) immune checkpoint inhibitor to demonstrate superiority, including better tolerability, versus Yervoy, a standard of care in this patient population. Based on data from the CheckMate -238 trial, the National Comprehensive Cancer Network® (NCCN®) recently added nivolumab to its treatment guidelines for completely resected stage IIIIB/C melanoma and completely resected stage III melanoma with clinical satellite or in-transit metastases.6

In CheckMate -238, adverse events (AEs) leading to discontinuation were reported in 9% of Opdivo-treated patients
Yervoy 

metastatic melanoma. 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 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.

Bristol-Myers Squibb pioneered the use of immune checkpoint inhibitors for the adjuvant treatment of melanoma, beginning with Yervoy. Five-year overall survival data from the Phase 3 CA184-029 trial were recently added to the prescribing information for Yervoy for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. In the trial, 65% of patients treated with Yervoy were alive at five years, compared with 54% of patients who received placebo (HR: 0.72; 95% CI: 0.58-0.88; p <0.002). This analysis was conducted at a median follow-up of 5.3 years.

“Although there are approved therapies to help prevent melanoma recurrence, around seven out of 10 patients with stage III disease do not receive treatment following surgery,” said Valerie Guild, co-founder and president, AIM at Melanoma Foundation. “As an advocate, I have witnessed countless times the frustration and fear patients experience when their cancer returns – even after it was removed by surgery. Today’s approval offers new hope for people with melanoma that their disease may not come back.”

**About the Pivotal CheckMate -238 Study**

CheckMate -238 is an ongoing Phase 3, randomized double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of stage III/B/C or stage IV melanoma. The trial randomized 906 patients 1:1 to receive either OPDIVO 3 mg/kg every two weeks (n=453) or Yervoy 10 mg/kg (n=453) every three weeks for four doses and then every 12 weeks starting at week 24. Patients were treated until disease recurrence, unacceptable toxicity or consent withdrawal for up to one year. The primary endpoint is RFS defined as the time between randomization and the date of first recurrence, new primary melanoma or death. After meeting the primary endpoint, the trial will continue to evaluate for overall survival, a secondary endpoint. Interim data were presented at the European Society for Medical Oncology 2017 Congress in Madrid, Spain, with simultaneous publication in The New England Journal of Medicine.

**Select Safety Profile from the CheckMate -238 Trial**

The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions, reported in at least 20% of OPDIVO-treated patients, were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colic (6%) and hepatitis (3%).

**About the CA184-029 Study**

The Phase 3 CA184-029 trial, a randomized (1:1), double-blind, placebo-controlled study, investigated the use of Yervoy for the adjuvant treatment of melanoma. A total of 951 enrolled patients with resected stage IIIA (>1 mm nodal involvement), IIIB and IIC (with no in-transit metastases) melanoma received either Yervoy 10 mg/kg (n=475) or placebo (n=476) every three weeks for four doses, followed by every 12 weeks from week 24 to week 156 or until documented disease recurrence or unacceptable toxicity. The major efficacy outcomes were independent review committee-assessed RFS and OS. Yervoy reduced the risk of recurrence or death by 25% versus placebo (HR: 0.75; 95% CI: 0.64 to 0.90; p <0.002). Median RFS was 26 months for Yervoy (95% CI: 19 to 39) and 17 months for placebo (95% CI: 13 to 22). There were 234 RFS events in the Yervoy arm (49% of patients; 220 recurrences, 14 deaths) and 294 events in the placebo arm (62% of patients; 289 recurrences, 5 deaths).

**Select Safety Profile from the CA184-029 Trial**

In the CA184-029 trial, severe to fatal immune-mediated adverse reactions were reported, and included enterocolitis (16%), hepatitis (11%), endocrinopathy (8%), hypopituitarism (7%), dermatitis (4%), neuropathy (1.7%), hyperthyroidism (0.6%), meningitis (0.4%), primary hypothyroidism (0.2%), myocarditis (0.2%), pericarditis (0.2%), pneumonitis (0.2%), and uveitis (0.2%). The most common adverse reactions were rash (50%), diarrhea (49%), fatigue (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%). Yervoy was discontinued for adverse reactions in 52% of patients.

INDICATIONS

OPDVO® (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), 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 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 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.

OPDIVO® (nivolumab) is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

OPDIVO (10 mg/mL) is an injection for intravenous (IV) use.

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 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, increases to >3 and up to 5 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 elevations >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 0.6% (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% (89/407) 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, 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
necrosis. 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 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 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 dose 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 037, 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 ODPIVO dose, 2 from infection 8 to 9 months after completing ODPIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving ODPIVO (n=236). The most frequent serious adverse reactions reported in at least 2% of patients receiving ODPIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving ODPIVO (n=270). The most frequent serious adverse reactions reported in at least 2% of patients receiving ODPIVO 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, asthenia, back pain, general physical health deterioration, abdominal pain, and pneumonia. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of ODPIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of ODPIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of ODPIVO-treated patients.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with ODPIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with ODPIVO (n=206) vs 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 ODPIVO 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 ODPIVO arm (n=313) were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving ODPIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving ODPIVO (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 ODPIVO (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 ODPIVO (n=236) 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 ODPIVO (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 ODPIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). In Checkmate 238, the most common adverse reactions (≥20%) reported in ODPIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colic/lots (6%), and hepatitis (3%). The most common adverse reactions (≥20%) in patients who received ODPIVO 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, pyrexia, headache, and abdominal pain.

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 067–advanced melanoma alone or in combination with YERVOY® (ipilimumab); 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; Checkmate 238–adjuvant treatment of melanoma

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

Indications and Important Safety Information for YERVOY ® (ipilimumab)

Indications

YERVOY® (ipilimumab) is indicated for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

YERVOY (5 mg/mL) is an injection for intravenous (IV) use.

Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY (ipilimumab) 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.

Recommended Dose Modifications

Endocrine: Withhold YERVOY for symptomatic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY in patients with severe endocrinopathy (Grade 2-4) and who are receiving <7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY in patients with severe immune-mediated ophthalmologic reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

Immune-mediated Enterocolitis

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent). Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3-5 days or recurring after symptom improvement. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 enterocolitis occurred in 68 patients (14%). Seven (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications.

Immune-mediated Hepatitis

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY. Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution. Withhold YERVOY in patients with Grade 2 hepatotoxicity. Permanently discontinue YERVOY in patients with Grade 3-4 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-4 immune-mediated hepatitis occurred in 51 patients (11%) and moderate Grade 2 immune-mediated hepatitis occurred in 22 patients (5%). Liver biopsy performed in 6 patients with Grade 3-4 hepatitis showed evidence of toxic or autoimmune hepatitis.

Immune-mediated Dermatitis

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Treat mild to moderate dermatitis [e.g., localized rash and pruritus] symptomatically; administer topical or systemic corticosteroids if there is no improvement within 1 week. Withhold YERVOY in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-4 immune-mediated dermatitis occurred in 19 patients (4%). There were 99 patients (21%) with moderate Grade 2 dermatitis.

Immune-mediated Neuropathies

Immune-mediated neuropathies, including fatal cases, can occur with YERVOY. Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities). Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities), such as Guillain-Barre-like syndromes. Institute medical intervention as appropriate for management for severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-5 immune-mediated neuropathy occurred in 8 patients (2%); the sole fatality was due to complications of Guillain-Barré syndrome. Moderate Grade 2 immune-mediated neuropathy occurred in 1 patient (0.2%).

Immune-mediated Endocrinopathies

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY. Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients
may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternative etiology has been identified, signs or symptoms should be considered immune-mediated. Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold YERVOY in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-4 immune-mediated endocrinopathies occurred in 39 patients (8%) and Grade 2 immune-mediated endocrinopathies occurred in 93 patients (20%). Of the 39 patients with Grade 3-4 immune-mediated endocrinopathies, 35 patients had hypopituitarism (associated with 1 or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 3 patients had hyperthyroidism, and 1 had primary hypothyroidism. The median time to onset of Grade 3-4 immune-mediated endocrinopathy was 2.2 months (range: 2 days-8 months). Twenty-seven (69.2%) of the 39 patients were hospitalized for immune-mediated endocrinopathies. Of the 93 patients with Grade 2 immune-mediated endocrinopathy, 74 had primary hypopituitarism (associated with 1 or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 9 had primary hypothyroidism, 3 had hyperthyroidism, 3 had thyroiditis with hypo- or hyperthyroidism, 2 had hypogonadism, 1 had both hyperthyroidism and hypopituitarism, and 1 subject developed Graves’ ophthalmopathy. The median time to onset of Grade 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days-19.3 months).

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. 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 YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss. In Trial 2, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients unless specified: eosinophilia (2.1%), pancreatitis (1.3%), meningitis, pneumonitis, sarcoidosis, pericarditis, uveitis, and fatal myocarditis.

Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with <1% incidence: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, hemolytic anemia, and nephritis.

Embryo-fetal Toxicity

Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY.

Lactation

It is not known whether YERVOY is secreted in human milk. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

Common Adverse Reactions

The most common adverse reactions (≥5%) in patients who received YERVOY at 10 mg/kg were rash (50%), diarrhea (49%), fatigue (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%).

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

About the Opdivo Clinical Development Program

Bristol-Myers Squibb’s global development program is founded on scientific expertise in the field of Immuno-Oncology and includes a broad range of clinical trials studying Opdivo, across all phases, in a variety of tumor types. To date, the Opdivo clinical development program has enrolled more than 25,000 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’ 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 Bristol-Myers Squibb’s Patient Access Support**

Bristol-Myers Squibb remains committed to providing assistance so that cancer patients who need our medicines can access them and expedite time to therapy.

BMS Access Support®, the Bristol-Myers Squibb patient access and reimbursement program, is designed to help appropriate patients initiate and maintain access to BMS medicines during their treatment journey. BMS Access Support offers benefit investigation, prior authorization assistance and co-pay assistance for eligible, commercially insured patients. More information about our access and reimbursement support can be obtained by calling BMS Access Support® at 1-800-861-0048 or by visiting www.bmsaccesssupport.com.

**About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration**

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Bristol-Myers Squibb expanded its territorial rights to develop and commercialize Opdivo globally except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Ono and Bristol-Myers Squibb further expanded the companies’ strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

**Bristol-Myers Squibb Forward-Looking Statement**

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors 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.

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**References**


**Language:**

English

**Contact:**

Bristol-Myers Squibb
FDA approves $BMY adjuvant tx for patients w/fully resected melanoma w/lymph node involvement or metastatic disease: