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Phase III CheckMate -067 Trial Demonstrates Superior Progression-Free Survival of *Opdivo+Yervoy* Regimen or *Opdivo* Monotherapy vs. *Yervoy* Monotherapy in Previously Untreated Patients with Advanced Melanoma

(PRINCETON, NJ, May 31, 2015) – Bristol-Myers Squibb Company (NYSE: BMY) announced positive results of a Phase III trial (CheckMate -067) evaluating the Opdivo (nivolumab)+Yervoy (ipilimumab) regimen or Opdivo monotherapy vs. Yervoy monotherapy in patients with previously untreated advanced melanoma.

Through the collaboration agreement entered into in September 2011 between ONO and BMS, ONO granted BMS exclusive rights to develop and commercialize Opdivo in the rest of the world, except in Japan, Korea and Taiwan where ONO had retained all rights to develop and commercialize the compound. In July 2014, ONO and BMS signed a new collaboration agreement in which the companies agreed to jointly develop and commercialize Opdivo, ipilimumab and three early-stage immunotherapies in Japan, South Korea and Taiwan.

In USA, Opdivo was approved under accelerated approval for the treatment of unresectable or metastatic melanoma and disease progression following Yervoy and, if BRAF V600 mutation positive, a BRAF inhibitor in December 2014 and approved for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy in March 2015. Also, BMS has a robust clinical development program in a variety of tumor types overseas, including: Renal Cell Carcinoma (RCC), Head and Neck Cancer, Blood Cancer, Glioblastoma, Colorectal Cancer, Pancreatic Cancer, Gastric Cancer, Hepatocellular Carcinoma, Triple-Negative Breast Cancer, Small-Cell Lung Cancer, Bladder Cancer. In Japan, ONO launched it for the treatment of unresectable melanoma in September 2014. Also, ONO is conducting clinical development programs including RCC, NSCLC, Head and Neck Cancer, Gastric Cancer, Esophageal Cancer, Hepatocellular Carcinoma and Hodgkin Lymphoma.

Attached from the following page is the press release made by BMS for your information.

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Bristol-Myers Squibb

Phase III CheckMate -067 Trial Demonstrates Superior Progression-Free Survival of *Opdivo+Yervoy* Regimen or *Opdivo* Monotherapy vs. *Yervoy* Monotherapy in Previously Untreated Patients with Advanced Melanoma

Both the* Opdivo+Yervoy *regimen and* Opdivo *monotherapy showed superior progression-free survival and objective response rate vs.* Yervoy *monotherapy

Opdivo+Yervoy *regimen showed improved outcomes vs. Opdivo monotherapy in PD-L1 non- and low-expressers (<5%)*

Safety profile of the* Opdivo+Yervoy *regimen from this trial was consistent with previously-reported studies

Results of CheckMate -067 presented as first abstract in the Plenary Session of the 51st Annual Meeting of the American Society of Clinical Oncology, and simultaneously published in New England Journal of Medicine

(PRINCETON, NJ, May 31, 2015) – Bristol-Myers Squibb Company (NYSE: BMY) today announced positive results of a Phase III trial (CheckMate -067) evaluating the *Opdivo* (nivolumab)+*Yervoy* (ipilimumab) regimen or *Opdivo* monotherapy vs. *Yervoy* monotherapy in patients with previously untreated advanced melanoma. Both the *Opdivo+Yervoy* regimen (n=314) and *Opdivo* monotherapy (n=316) demonstrated superiority to *Yervoy* (n=315), the current standard of care, for the co-primary endpoint of progression-free survival (PFS). Median PFS was 11.5 months for the *Opdivo+Yervoy* regimen and 6.9 months for *Opdivo* monotherapy, vs. 2.9 months for *Yervoy* monotherapy. The *Opdivo+Yervoy* regimen demonstrated a 58% reduction in the risk of disease progression vs. *Yervoy* (hazard ratio: 0.42; 99.5% CI, 0.31 to 0.57; P<0.0001), while *Opdivo* monotherapy demonstrated a 43% risk reduction versus *Yervoy* monotherapy (hazard ratio: 0.57; 99.5% CI, 0.43 to 0.76; P<0.00001). The hazard ratio for the exploratory endpoint comparing *Opdivo+Yervoy* PFS and *Opdivo* PFS was 0.74 (95% CI, 0.60 to 0.92). The safety profile was consistent with previously-reported studies evaluating the *Opdivo+Yervoy* regimen, and most treatment-related adverse events were resolved using established algorithms. The treatment-related adverse event rate was 95.5% for the *Opdivo+Yervoy* regimen compared to 82.1% for *Opdivo* monotherapy and 86.2% for *Yervoy* monotherapy. Most select treatment-related adverse events were resolved using established management guidelines. The trial is ongoing and patients continue to be followed for overall survival (OS), a co-primary endpoint.

These data will be presented in today's Plenary Session at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO) at 1:35 – 1:50 p.m. CDT and featured during an ASCO press briefing (Late Breaking Abstract #1) at 8:00 – 9:00 a.m.. CDT. The trial results were also published today in the *New England Journal of Medicine.* CheckMate -067 is the second randomized trial to show clinical benefit of the *Opdivo+Yervoy* regimen in previously untreated advanced melanoma.

"A significant milestone in cancer research, Checkmate -067 is the first Phase III trial to demonstrate improved outcomes for a PD-1 immune checkpoint inhibitor administered as monotherapy and in combination with another Immuno-Oncology agent vs. the standard of care for treatment of first-line patients with advanced melanoma," said Jedd D. Wolchok, MD, PhD, Chief of the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center. "The trial also provided critical insight into the relationship between PD-L1 expression and treatment with these agents with respect to progression-free survival. The *Opdivo+Yervoy* regimen significantly improved progression-free survival for patients whose tumors are low- or non-expressers of PD-L1, as compared to *Opdivo* or *Yervoy* monotherapy. This finding offers a clearer path for clinicians considering the most appropriate Immuno-Oncology treatment approach for a patient."

Based on sub-analyses, the CheckMate -067 trial also allows for better understanding of the efficacy of the *Opdivo+Yervoy* regimen based on PD-L1 expression in patient tumors. In the trial, the *Opdivo+Yervoy* regimen demonstrated numerically longer PFS and a higher objective response rate (ORR) than *Opdivo* monotherapy in the overall population. Based on tumor PD-L1 expression, the greatest benefit of the regimen in PFS and ORR was seen in PD-L1 low- and non-expressing tumors.

"As individual agents, *Opdivo* and *Yervoy* each have transformed the treatment of advanced melanoma and helped to redefine survival expectations for patients with advanced melanoma," said Michael Giordano, senior vice president, Head of Development, Oncology, Bristol-Myers Squibb. "Our development strategy has aimed to characterize the potential of *Opdivo* and *Yervoy* as part of a regimen to improve outcomes in patients with this disease. The findings of Checkmate -067 validate our strategy to combine Immuno-Oncology agents as the best approach to offer patients the potential for long-term survival."

About CheckMate -067

CheckMate -067 is a Phase III, double-blind, randomized study that evaluated the *Opdivo +Yervoy* regimen or *Opdivo* monotherapy vs. *Yervoy* monotherapy in patients with previously untreated advanced melanoma. The trial enrolled 945 patients who were randomized to receive the

Opdivo+*Yervoy* regimen (n=314), *Opdivo* monotherapy (n=316) or *Yervoy* monotherapy (n=315). Baseline disease characteristics, including BRAF mutation and PD-L1 status, were balanced across the 3 treatment groups.

- Patients in the *Opdivo*+*Yervoy* regimen group received 1 mg/kg of *Opdivo* plus 3 mg/kg of *Yervoy* every 3 weeks for 4 doses followed by 3 mg/kg of *Opdivo* every 2 weeks for cycle 3 and beyond
- In the *Opdivo* monotherapy group, patients were treated with 3 mg/kg of *Opdivo* every 2 weeks plus *Yervoy*-matched placebo
- In the *Yervoy* monotherapy group, patients were treated with 3 mg/kg of *Yervoy* per every 3 weeks for 4 doses plus *Opdivo*-matched placebo

Patients were treated until progression or unacceptable toxic effects. The minimum follow-up period after randomization was 9 months. Patients continue to be followed for OS.

The co-primary endpoints were PFS and OS. Formal statistical analysis compared the combination regimen and *Opdivo* monotherapy to *Yervoy*. Exploratory analysis comparing the regimen to *Opdivo* was also conducted. In addition, exploratory analyses of PFS and ORR were conducted based upon PD-L1 expression. Exploratory endpoints include duration of objective response and safety/tolerability of study drug therapy.

The results comparing the *Opdivo*+*Yervoy* regimen to *Yervoy* monotherapy and *Opdivo* monotherapy to *Yervoy* monotherapy were consistently observed irrespective of BRAF status, PD-L1 expression, and metastasis stage.

In addition, the *Opdivo*+*Yervoy* regimen and *Opdivo* monotherapy demonstrated higher ORR (57.6% and 43.7%, respectively) vs. *Yervoy* monotherapy (19%). The percentage of patients with a complete response was 11.5, 8.9 and 2.2, favoring the regimen over *Opdivo* monotherapy or *Yervoy* monotherapy. Time to objective response was similar in each group and the median duration of response was not reached in any of the groups.

Among patients with high PD-L1 expression (≥5%), ORR was 72.1% (95% CI, 59.9 to 82.3), 57.5% (95% CI, 45.9 to 68.5) and 21.3% (95% CI, 12.7 to 32.3) for the *Opdivo*+*Yervoy* regimen, *Opdivo* monotherapy and *Yervoy* monotherapy groups, respectively. In patients whose tumors expressed <5% PD-L1, the ORR was 54.8% (95% CI, 47.8 to 61.6), 41.3% (95% CI, 34.6 to 48.4) and 17.8% (95% CI, 12.8 to 23.8). Of note, comparable ORR was seen using the regimen in PD-L1 low- or non-expressing patients to those observed using *Opdivo* monotherapy in PD-L1-expressing patients.

CheckMate -067 further characterized the safety profile of the *Opdivo*+*Yervoy* regimen or *Opdivo* monotherapy versus *Yervoy* monotherapy. The safety profile was consistent with that previously

reported for the *Opdivo+Yervoy* regimen. The treatment-related adverse event rate was higher (95.5%) for the *Opdivo+Yervoy* regimen compared to 82.1% for *Opdivo* monotherapy and 86.2% for *Yervoy* monotherapy. The incidence of grade 3/4 adverse events (drug-related AEs) was higher with the *Opdivo+Yervoy* regimen (55.0%) compared to 16.3% of patients who received *Opdivo* monotherapy and 27.3% of patients who received *Yervoy* monotherapy. The most common grade 3/4 AEs with the *Opdivo+Yervoy* regimen were diarrhea (9.3%), colitis (7.7%), increased alanine aminotransferase (8.3%), and increased aspartate aminotransferase (6.1%). The *Opdivo+Yervoy* regimen was discontinued due to adverse events in 36.4% of patients versus 7.7% for *Opdivo* monotherapy and 14.8% for *Yervoy* montherapy. Resolution rates for grade 3 or 4 select adverse events were between 85 and 100% in the combination group for most organ categories. Of the patients who discontinued treatment due to adverse events, 68% of patients experienced either complete or partial response. There were no drug-related deaths associated with the *Opdivo+Yervoy* regimen. One drug-related death was reported in the *Opdivo* group (neutropenia) and one was reported in the *Yervoy* group (cardiac arrest), although such adverse events have not been associated with these drugs in prior studies.

About *Opdivo* and *Yervoy*

Cancer cells may exploit "regulatory" pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack. *Opdivo* and *Yervoy* are both monoclonal antibodies and immune checkpoint inhibitors that target separate, distinct checkpoint pathways. Inhibition of these immune checkpoint pathways results in enhanced T-cell function greater than the effects of either antibody alone.

Opdivo became the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world on July 4, 2014 when Ono Pharmaceutical Co. announced that it received manufacturing and marketing approval in Japan for the treatment of patients with unresectable melanoma. In the U.S., the Food and Drug Administration (FDA) granted its first approval for *Opdivo* for the treatment of patients with unresectable or metastatic melanoma and disease progression following *Yervoy* (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor. Recently, on March 4, 2015, *Opdivo* received its second FDA approval for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

On March 25, 2011, the FDA approved *Yervoy* 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. *Yervoy* is now approved in more than 40 countries.

Bristol-Myers Squibb has a broad, global development program to study *Opdivo* in multiple tumor types consisting of more than 50 trials – as monotherapy or in combination with other therapies – in which more than 8,000 patients have been enrolled worldwide.

IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis

- Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO; no cases occurred in Trial 1 or Trial 3. In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis occurred in 2.2% (6/268) of patients receiving OPDIVO; one with Grade 3 and five with Grade 2. In Trial 3, immune-mediated pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO, including, five Grade 3 and two Grade 2 cases. Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold OPDIVO until resolution for Grade 2.

Immune-Mediated Colitis

- In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis occurred in 2.2% (6/268) of patients receiving OPDIVO; five with Grade 3 and one with Grade 2. In Trial 3, diarrhea occurred in 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated colitis occurred in 0.9% (1/117) of patients. Monitor patients for immune-mediated colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3. Permanently discontinue OPDIVO for Grade 4 colitis or recurrent colitis upon restarting OPDIVO.

Immune-Mediated Hepatitis

- In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs 12%), alkaline phosphatase (22% vs 13%), ALT (16% vs 5%), and total bilirubin (9% vs 0). Immune-mediated hepatitis occurred in 1.1% (3/268) of patients receiving OPDIVO; two with Grade 3 and one with Grade 2. In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4 immune-mediated hepatitis.

Immune-Mediated Nephritis and Renal Dysfunction

- In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients. In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 serum creatinine elevation, withhold OPDIVO and administer corticosteroids; if worsening or no improvement

occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO.

Immune-Mediated Hypothyroidism and Hyperthyroidism

- In Trial 1, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. In Trial 3, hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. Hyperthyroidism occurred in 1.7% (2/117) of patients, including one Grade 2 case. Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism.

Other Immune-Mediated Adverse Reactions

- In Trial 1 and 3 (n=385), the following clinically significant immune-mediated adverse reactions occurred in <2% of OPDIVO-treated patients: adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyeliniation, autoimmune neuropathy, motor dysfunction, and vasculitis. Across clinical trials of OPDIVO administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome. Based on the severity of adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone- replacement therapy.

Embryofetal Toxicity

- Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO.

Lactation

- It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment.

Serious Adverse Reactions

- In Trial 1, serious adverse reactions occurred in 41% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.
- In Trial 3, serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse drug reactions reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Common Adverse Reactions

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

Please see U.S. Full Prescribing Information for OPDIVO at www.bms.com.

YERVOY® (ipilimumab) INDICATION & IMPORTANT SAFETY INFORMATION

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. 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) and thyroid function tests at baseline and before each dose.

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

Recommended Dose Modifications

Withhold dose for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving <7.5 mg prednisone or equivalent per day.

Permanently discontinue YERVOY for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day
- Failure to complete full treatment course within 16 weeks from administration of first dose
- Severe or life-threatening adverse reactions, including any of the following:
    - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥7 over baseline), stool incontinence, need for intravenous hydration for >24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
    - AST or ALT >5 × the upper limit of normal (ULN) or total bilirubin >3 × the ULN

- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full-thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations
- Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Severe immune-mediated reactions involving any organ system
- Immune-mediated ocular disease which is unresponsive to topical immunosuppressive therapy

Immune-mediated Enterocolitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, 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%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) patients
- Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis
- Infliximab was administered to 5 of 62 (8%) patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids
- 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
- 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
- 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)

Immune-mediated Hepatitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, 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%
- 13 (2.5%) additional YERVOY-treated patients experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5x but ≤5x the ULN or total bilirubin elevation >1.5x but ≤3x the ULN; Grade 2)
- 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
- Permanently discontinue YERVOY in patients with Grade 3-5 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

- Withhold YERVOY in patients with Grade 2 hepatotoxicity
- In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID)

Immune-mediated Dermatitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., 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
- There were 63 (12%) YERVOY-treated patients with moderate (Grade 2) dermatitis
- 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
- 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. Withhold YERVOY in patients with moderate to severe signs and symptoms
- 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

Immune-mediated Neuropathies:

- In the pivotal Phase 3 study in YERVOY-treated patients, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported
- Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported
- Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré–like syndromes
- Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities)

Immune-mediated Endocrinopathies:

- In the pivotal Phase 3 study in YERVOY- treated patients, 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
- Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) YERVOY-treated patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome
- Median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of 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 alternate etiology has been identified, signs or symptoms should be considered immune-mediated
    - Monitor thyroid function tests and clinical chemistries 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. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. Long-term hormone replacement therapy may be necessary

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations:

- In the pivotal Phase 3 study in YERVOY-treated patients, clinically significant immune-mediated adverse reactions seen in <1% were: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia
- Across the clinical development program for YERVOY, likely immune-mediated adverse reactions also reported with <1% incidence were: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, and ocular myositis
- 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

Pregnancy & Nursing:

- YERVOY is classified as pregnancy category C. There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus
- Human IgG1 is known to cross the placental barrier and YERVOY is an IgG1; therefore, YERVOY has the potential to be transmitted from the mother to the developing fetus
- It is not known whether YERVOY is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY

Common Adverse Reactions:

- 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 Full Prescribing Information, including **Boxed WARNING regarding immune-mediated adverse reactions,** available at www.bms.com.

Yervoy is a registered trademark of Bristol-Myers Squibb Company.

About Advanced Melanoma

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin. Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to the other organs, such as the lymph nodes, lungs, brain or other areas of the body. The incidence of melanoma has been increasing for at least 30 years. In 2015, an estimated 73,870 melanoma cases will be diagnosed in the U.S. Melanoma is mostly curable when treated in its early stages. However, in its late stages, the average survival rate is just 6 months with a 1-year survival of 25.5%, making it one of the most aggressive forms of cancer.

Immuno-Oncology at Bristol-Myers Squibb

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

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

cancer, including researching the potential of combining Immuno-Oncology agents that target different pathways in the treatment of cancer.

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

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that the combination treatment of Opdivo and Yervoy will receive regulatory approval or, if approved, that it will become a commercially successful regimen. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2014 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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