Yervoy (ipilimumab) Improves Overall Survival in Fully Resected Stage III Melanoma Patients From Phase 3 Study

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Yervoy demonstrated a 28% reduction in the risk of death versus placebo in first disclosure of overall survival data from pivotal study CA184-029 (EORTC 18071)

Risk of distant metastasis was reduced by 24% with Yervoy compared to placebo

With longer follow-up, the recurrence-free survival benefit and safety profile remained consistent with the previously reported primary analysis

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) announced today superior efficacy with Yervoy 10 mg/kg versus placebo on all survival endpoints in the Phase 3 trial CA184-029 (EORTC 18071) evaluating stage III melanoma patients who are at high risk of recurrence following complete surgical resection. In the study, Yervoy compared with placebo significantly improved overall survival (OS) (HR=0.72 [95.1% CI: 0.58-0.88; p=0.001]), a secondary endpoint, with five-year OS rates at 65.4% in the Yervoy group and 54.4% in the placebo group. Distant metastasis-free survival (DMFS), a secondary endpoint, was also significantly improved versus placebo (HR=0.76 [95.8% CI: 0.64-0.92; p=0.002]) and had five-year DMFS rates of 48.3% and 38.9% in the Yervoy and placebo groups, respectively. In this updated five-year analysis, the recurrence-free survival (primary endpoint) benefit observed previously with Yervoy was maintained (HR=0.76 [95% CI: 0.64-0.89; p<0.001]). The safety profile remained consistent with the initial analysis, with no new deaths or safety signals. The most common grade 3/4 immune-related adverse events in the Yervoy group were gastrointestinal (16.1%), hepatic (10.8%), and endocrine (7.9%).

These data were featured today, October 8, during the 2016 European Society for Medical Oncology Congress Press Program and simultaneously published in The New England Journal of Medicine. The data will also be presented today during a Presidential Symposium from 5:00-5:15 p.m. CEST (Abstract #LBA2_PR).

“Despite surgical intervention, most patients with stage III melanoma experience disease recurrence and progress to metastatic disease, reinforcing the unmet need for effective systemic therapies in the adjuvant setting,” said Alexander M.M. Eggermont, M.D., Ph.D., director general, Cancer Institute Gustave Roussy in Villejuif, France. “The impact of Yervoy on overall survival, distant-metastasis free survival, and recurrence-free survival observed in study-029 offers physicians new insights in the treatment of adjuvant melanoma.”

In stage III melanoma, the disease has not yet spread to distant lymph nodes or to other parts of the body and requires surgical resection of the primary tumor as well as the involved lymph nodes. The stage III patient population is heterogeneous with disease-specific survival rates of 78%, 59%, and 40% for stage IIIA, IIIB, and IIIC melanoma, respectively.

“The results from study-029 are important data for the scientific community and underscore our ongoing dedication to improving survival across stages of melanoma,” said Vicki Goodman, M.D., development lead, Melanoma and Genitourinary Cancers, Bristol-Myers Squibb. “Yervoy is the first immune checkpoint inhibitor to demonstrate a statistically significant survival benefit for high-risk patients with fully resected stage III melanoma. With further evaluation of our Immuno-Oncology agents and different dosing options, we remain committed to further research across the full continuum of melanoma treatment.”

About CA184-029 (EORTC 18071)
Yervoy is approved for unresectable or metastatic melanoma. 4). CTLA-4 is a negative regulator of T-cell activity. The safety profile of Yervoy based on this updated analysis was consistent with previously reported findings from CA184-029 (EORTC 18071). In those initial findings, five patient deaths occurred due to drug-related adverse events (AE); no new deaths have since been reported. Among the 471 patients who received Yervoy, 465 (98.7%) experienced an AE of any grade, and 255 patients (54.1%) experienced a grade 3 or 4 AE, whereas among 474 placebo-treated patients, 432 (91.1%) experienced an AE of any grade, and 124 patients (26.2%) experienced a grade 3 or 4 AE. Immune-related AEs were more frequent with Yervoy than with placebo. The most common grade 3/4 immune-related AEs in the Yervoy group were gastrointestinal (16.1%), hepatic (10.8%), and endocrine (7.9%). The median time to onset of on-study grade 2-5 immune-related AEs ranged from 4.0 weeks (skin immune-related adverse events) to 13.1 weeks (neurological immune-related adverse events). Endocrine grade 2-4 immune-related AEs resolved in 51.5% of patients, and median time to resolution was 54.3 weeks. The majority (82-97%) of all other grade 2-4 immune-related AEs resolved, and median time to resolution ranged from 4.0 to 8.0 weeks.

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. Melanoma is separated into five staging categories (Stages 0-IV) based on the in-situ feature, thickness, and ulceration of the tumor, whether the cancer has spread to the lymph nodes, and how far the cancer has spread beyond lymph nodes. Stage III melanoma has reached the regional lymph nodes but has not yet spread to distant lymph nodes or to other parts of the body (metastasized) and requires surgical resection of the primary tumor as well as the local lymph nodes.

Bristol-Myers Squibb: At the Forefront of Immuno-Oncology Science & Innovation
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 that will raise survival expectations in hard-to-treat cancers and will change the way patients live with cancer.

We are leading the scientific understanding of I-O through our extensive portfolio of investigational and approved agents, including the first combination of two I-O agents in metastatic melanoma, and our differentiated clinical development program, which is studying broad patient populations across more than 20 types of cancers with 11 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs uniquely position us to advance the science of combinations across multiple tumors and potentially deliver the next wave of I-O combination regimens 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 inform which patients will benefit most from I-O therapies.

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 Yervoy
Yervoy is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activity. Yervoy binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response. On March 25, 2011, the U.S. Food and Drug Administration (FDA) approved Yervoy 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. Yervoy is approved for unresectable or metastatic melanoma in more than 50 countries from the EORTC’s pan-European network and specialized infrastructure. The trial enrolled eligible patients, which included those ≥18 years of age who underwent complete resection of stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis). In the trial, patients were randomized to receive Yervoy 10 mg/kg (n=476) or placebo (n=476) as an intravenous infusion every 3 weeks for 4 doses, followed by Yervoy 10 mg/kg or placebo every 12 weeks from Week 24 to Week 156 (three years), or until documented disease recurrence or unacceptable toxicity. Yervoy was studied across a broad range of patient characteristics, including patients with stage IIIa with lymph node >1 mm (20%), IIIb (44%) or IIIc with no in-transit metastases (36%); 42% had ulcerated primary lesions, and 58% had macroscopic lymph node involvement.

The primary endpoint was recurrence-free survival (RFS), defined as the time between the date of randomization and the date of first recurrence or death, as assessed by the Independent Review Committee. This analysis was the basis of the Yervoy approval in the United States for adjuvant treatment of melanoma at a dose of 10 mg/kg in October 2015. Secondary endpoints include overall survival (OS), distant metastases-free survival (DMFS), safety and health-related quality of life.

In the study, Yervoy significantly improved RFS, the primary endpoint, versus placebo across all patient groups. Updated five-year results demonstrated RFS remained significantly longer for Yervoy versus placebo, with a median RFS of 27.6 months (95% CI: 19.3-37.2) versus 17.1 months (95% CI: 13.6-21.6), respectively (HR=0.76; 95% CI: 0.64-0.89; p<0.001).

Yervoy also demonstrated a significant improvement in OS, a secondary endpoint of the study, with a 28% reduction in the risk of death versus placebo (HR=0.72 [95% CI: 0.58-0.88; p=0.001]) and an estimated five-year OS rate of 65.4% (95% CI: 60.8-69.6) for Yervoy versus 54.4% (95% CI: 49.7-58.9) for placebo. In addition, Yervoy showed a 24% reduction in the risk of developing distant metastases versus placebo (HR=0.76 [95.8% CI: 0.64-0.92; p=0.002]), with an estimated five-year DMFS rate of 48.3% with Yervoy versus 38.9% with placebo. The median DMFS was 48.3 months with Yervoy versus 27.5 months with placebo.

The safety profile of Yervoy also demonstrated a significant improvement in OS, with a 28% reduction in the risk of death versus placebo (HR=0.72 [95% CI: 0.58-0.88; p=0.001]) and an estimated five-year OS rate of 65.4% (95% CI: 60.8-69.6) for Yervoy versus 54.4% (95% CI: 49.7-58.9) for placebo. In addition, Yervoy showed a 24% reduction in the risk of developing distant metastases versus placebo (HR=0.76 [95.8% CI: 0.64-0.92; p=0.002]), with an estimated five-year DMFS rate of 48.3% with Yervoy versus 38.9% with placebo. The median DMFS was 48.3 months with Yervoy versus 27.5 months with placebo.
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.

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

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.

Recommended Dose Modifications

Endocrine: Withhold YERVOY for systemic 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 for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment. 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 3 mg/kg in Trial 1, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). 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 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids. 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 3 mg/kg in Trial 1, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5× the ULN or total bilirubin elevations >3× the ULN; Grade 3-5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4%. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5× but ≤5× the ULN or
total bilirubin elevation >1.5 x but ≤3x the ULN; Grade 2). 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). 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 3 mg/kg in Trial 1, 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, and hemorrhagic manifestations) occurred in 13 YERVOY-treated patients (2.3%); 1 patient (0.2%) died as a result of toxic epidermal necrolysis and 1 additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis. 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 3 mg/kg in Trial 1, 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. 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 alternate etiology has been identified, signs or symptoms should be considered immune-mediated. Monitor clinical chemistries, adrenocorticotrophic 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 3 mg/kg in Trial 1, 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 YERVOY-treated patients (1.8%). All 9 patients had hypophysitis, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing’s syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY. 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 endocrinopathy, 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 immunsuppressive therapy. In Trial 1, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia. 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 hypoacusis, 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 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%). 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 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, 2015 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

**Language:**

English

**Contact:**

Bristol-Myers Squibb Company
Media:
Audrey Abernathy, 919-605-4521
audrey.abernathy@bms.com
or
Investors:
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com

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