U.S. Food and Drug Administration Expands Approval of Yervoy® (ipilimumab) to Include Pediatric Patients 12 Years and Older with Unresectable or Metastatic Melanoma

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Yervoy showed a consistent safety profile and comparable drug levels across pediatric and adult patients

First Bristol-Myers Squibb immuno-oncology approval for adolescents 12 years and older reflects the company’s commitment to the pediatric cancer community

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that the U.S. Food and Drug Administration (FDA) has expanded the indication for Yervoy® (ipilimumab) injection for intravenous use to now include the treatment of unresectable or metastatic melanoma in pediatric patients 12 years of age and older. Yervoy was evaluated in two trials of pediatric patients: a dose-finding study in 33 patients aged two to 21 years with relapsed or refractory solid tumors and an open-label, single-arm trial in 12 adolescents (ages ranging from 12 to 16 years) with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma. The overall safety profile of Yervoy in children and adolescents was consistent with the safety profile in adults, and similarities in disease between adult and pediatric patients 12 years and older allow for extrapolation of data. Based on a population pharmacokinetic analysis, exposure in adolescents 12 years and older is comparable to that in adults for the approved dose of 3 mg/kg, administered intravenously over 90 minutes every three weeks for a total of four doses.1

Yervoy is associated with a Boxed Warning and can result in severe to 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. Please see below for additional Important Safety Information, including Boxed Warning regarding immune-mediated adverse reactions.

“When my daughter was diagnosed with melanoma, our entire family was devastated,” said Brenda Busby, mother to a 12-year-old patient and pediatric program coordinator, Melanoma Research Foundation. “As someone who has lived with the many challenges of pediatric cancer, I know how important it is for patients and their families who face metastatic melanoma to have access to new therapies.”

“Metastatic melanoma is extremely rare in children and adolescents, which makes it particularly difficult to investigate in clinical trials. Though designing clinical trials in small pediatric populations can be challenging, this group of investigators committed to bringing a new therapy to those in need,” said Lia Gore, MD, University of Colorado School of Medicine and Children’s Hospital of Colorado. “Ipilimumab’s approval represents the culmination of a long effort and gives physicians the ability to expand immuno-oncology – one of the most exciting areas of medicine – for the treatment of young adults with metastatic melanoma.”

The U.S. FDA approval for Yervoy in patients 12 years and older with metastatic melanoma marks Bristol-Myers Squibb’s first pediatric indication for an immuno-oncology medicine. The expanded indication builds upon six years of experience with Yervoy, which has been used to treat more than 38,000 adult patients with metastatic melanoma since its first approval.3

“Despite significant advancements in oncology research for adults in recent years, treatment options continue to be limited for pediatric patients with metastatic melanoma,” said Chris Boerner, PhD, president and head of U.S. commercial operations, Bristol-Myers Squibb. “At Bristol-Myers Squibb, we are committed to providing meaningful support to the pediatric oncology community. This latest approval of Yervoy exemplifies our ongoing effort to expand the availability of therapies for younger cancer patients.”
As part of its commitment to children and adolescents with cancer, Bristol-Myers Squibb continues to explore pediatric applications for investigational oncology agents within its broad development program. In addition, Bristol-Myers Squibb supports organizations and initiatives focused on pediatric patients and their families.

**About the Yervoy Studies in Pediatric Patients**

Yervoy has been evaluated in a total of 45 pediatric patients across two clinical trials. The safety and effectiveness of Yervoy have been established in pediatric patients 12 years and older. The use of Yervoy in this age group is supported by evidence from adequate and well-controlled studies of Yervoy in adults and population pharmacokinetic data demonstrating that the exposure at a dose of 3 mg/kg in the pediatric and adult populations is comparable. In addition, the tumor biology and the course of advanced melanoma is sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients.

In a dose-finding trial, Yervoy was evaluated in 33 pediatric patients with relapsed or refractory solid tumors. Patients enrolled in the study ranged from two to 21 years of age, with a median age of 13 years, and 20 of the patients were 12 years of age or older. Yervoy was administered at doses of 1, 3, 5 and 10 mg/kg intravenously over 90 minutes every three weeks for four doses and then every 12 weeks thereafter until progression or treatment discontinuation.

Yervoy was also evaluated in an open-label, single-arm trial in 12 pediatric patients 12 years and older with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma. Patients received Yervoy 3 mg/kg (four patients) or 10 mg/kg (eight patients) intravenously over 90 minutes every three weeks for four doses.

Of the 17 patients 12 years of age and older with melanoma treated with Yervoy across both studies, two patients experienced objective responses, including one partial response that was sustained for 16 months.

The approved dose for Yervoy in pediatric patients with unresectable or metastatic melanoma is 3 mg/kg, administered intravenously over 90 minutes every three weeks for a total of four doses.

**About the Population Pharmacokinetic Analysis**

Based on a population pharmacokinetic analysis using available pooled data from 565 patients from four phase 2 adult studies (N=521) and two pediatric studies (N=44), body weight normalized clearance of Yervoy is comparable between adult and pediatric subjects.

**Indications and Important Safety Information for YERVOY ® (ipilimumab)**

**Indications**

YERVOY® (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older).

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.

**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 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× but ≤3× the ULN; Grade 2). In a dose-finding trial, Grade 3 increases in transaminases with or without coexistent 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 LFTs (hepatic transaminase and bilirubin levels) and assess 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 (Grade 3-5). 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 YERVOY-treated patients (2.5%); 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-Barre 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-Barre 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. One patient (0.2%) died as a result of complications.

**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 non-specific 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,
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 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 hypopituitarism, 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 25 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 immunosuppressive therapy. In Trial 1, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients: nephritis, pneumonitis, menigitis, 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%), menigitis, 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: angioptathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune cranial 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%), diaphoresis (49%), fatigue (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%).

Other common adverse reactions were seen in <1% of YERVOY-treated patients unless specified: eosinophilia (2.1%), pancreatitis (1.3%), menigitis, 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: angioptathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune cranial neuropathy (encephalitis), myositis, polymyositis, ocular myositis, hemolytic anemia, and nephritis.

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

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 cancer with 14 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance the 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 a patient’s 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 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. There is a broad, ongoing development program in place for Yervoy spanning multiple tumor types.

About Bristol-Myers Squibb’s Patient Access Support

Bristol-Myers Squibb remains committed to providing a comprehensive set of programs and services 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 Services 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 services can be obtained by calling BMS Access Support® at 1-800-861-0048 or by visiting www.bmsaccesssupport.com.

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.