Phase 3 Study Evaluating Yervoy® (Ipilimumab) for Melanoma in an Adjuvant Setting Meets Primary Endpoint of Recurrence-Free Survival

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- Results demonstrate a significant improvement in recurrence-free survival for an investigational dose of Yervoy vs. placebo for patients with stage 3 melanoma at high risk of recurrence following surgical resection
- Types of adverse events were generally consistent with those observed using Yervoy in advanced melanoma, although a higher incidence of endocrinopathies was observed
- Third positive Phase 3 trial of Yervoy in melanoma, now with a study demonstrating efficacy in an earlier stage of the disease

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced results from a Phase 3 randomized, double blind study demonstrating that Yervoy (ipilimumab) 10 mg/kg (n=475) significantly improved recurrence-free survival (RFS, the length of time before recurrence or death) vs. placebo (n=476) for patients with stage 3 melanoma who are at high risk of recurrence following complete surgical resection, an adjuvant setting. A twenty-five percent reduction in the risk of recurrence or death was observed (HR = 0.75; 95% CI = 0.64–0.90; p = 0.0013). At three years, an estimated 46.5% of patients treated with Yervoy were free of disease recurrence compared to an estimated 34.8% of patients on placebo. The median RFS was 26.1 months for Yervoy vs. 17.1 months for placebo, with a median follow-up of 2.7 years. The data will be presented at the 50th Annual Meeting of the American Society of Clinical Oncology at 3:00 p.m. CDT today and highlighted at a Congress press briefing (LBA9008).

Treatment-related adverse events were common, with most being immune-related, and were managed using standard Yervoy adverse event (AE) management protocols. These Grade ≥3 AEs in the Yervoy and placebo arms, respectively, were gastrointestinal (15.9% vs. 0.8%), liver (10.6% vs. 0.2%), endocrine (8.5% vs. 0%) and dermatologic (4.5% vs. 0%). Most were managed and resolved using established algorithms. Per investigator assessment, the incidence of drug-related death in the Yervoy arm was 1.1% (n=5) and no drug-related deaths were observed in the placebo arm. Of the patients who began treatment with Yervoy (n=471), 48.8% (n=230) discontinued treatment due to drug-related AEs vs. 1.7% (n=8) in the placebo arm.

“Despite the strong likelihood of disease recurrence among stage 3 melanoma patients, there are very limited treatment options available to help reduce the risk of metastatic disease after surgery. There is only one class of therapies available to patients and this standard of care has remained largely unchanged over the last 20 years,” said Alexander Eggermont, director general, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, presenter of the results and lead author of the abstract. “These findings are significant not only because ipilimumab is the first immune-checkpoint inhibitor to demonstrate an improvement in recurrence-free survival in this earlier treatment setting, but also because this benefit was observed across all patient sub-groups, including those who were at highest risk of recurrence. These findings add to the growing body of data for ipilimumab, which is currently approved at 3 mg/kg for metastatic melanoma.”

“This is the third positive Phase 3 trial of Yervoy in melanoma, reflecting our commitment to seeking options to address unmet medical needs across stages of disease and lines of therapy for melanoma,” said Michael Giordano, senior vice president, Head of Development, Oncology & Immunosciences, Bristol-Myers Squibb. “These findings demonstrate, for the first time, that Yervoy has the potential to reduce the risk of cancer recurrence at an earlier stage of melanoma and support our belief that immuno-oncology may have broad applicability across lines of therapy and stages of the disease.”
Additional trials of Yervoy for melanoma in the adjuvant setting are ongoing, including a Phase 3 study sponsored by the U.S. National Cancer Institute and conducted by ECOG-ACRIN investigating Yervoy at doses of 3 mg/kg and 10 mg/kg, or high-dose interferon alfa-2b in patients with high-risk stage 3 and resectable stage 4 melanoma.

About Study -029

CA184-029 (EORTC 18071) is a randomized, double-blind Phase 3 trial sponsored by Bristol-Myers Squibb and conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), assessing the efficacy of Yervoy at the investigational dose of 10 mg/kg in preventing or delaying recurrence after complete resection of high-risk Stage 3 melanoma. The trial enrolled patients in the United States, Canada, Europe, Russia and Australia who underwent complete resection of stage 3 cutaneous melanoma, excluding lymph node metastasis ≤1 millimeter or in-transit metastasis. Patients had stage 3A (21%), 3B (45%) or 3C (35%) melanoma; 41% percent had ulcerated primary melanoma and 56% had macroscopic lymph node involvement. Patients were stratified by stage and region and were randomized 1:1 to receive Yervoy 10 mg/kg (n=475) or placebo (n=476) every 3 weeks for 4 doses, then every 3 months for up to 3 years until completion, disease recurrence, or unacceptable toxicity. The primary endpoint was recurrence-free survival, analyzed on the intent-to-treat population.

Adjuvant Therapy in Melanoma

Melanoma is separated into five staging categories (stages 0-4) 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 3 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 involved lymph nodes. Some patients may also be treated with adjuvant therapy, although adjuvant treatment options are very limited. Despite surgical intervention and possible adjuvant treatment, most patients experience disease recurrence and progress to metastatic disease. By five years, the majority of stage 3B and 3C patients (68% and 89%, respectively) and a third of stage 3A patients (37%) have experienced disease recurrence.

About Yervoy

Yervoy, which is a recombinant, human monoclonal antibody, blocks the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activation. 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. The mechanism of action of Yervoy’s effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses. 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.

There is a broad, ongoing development program in place for Yervoy spanning multiple tumor types. This includes Phase 3 trials in prostate and lung cancers.

YERVÖ® (ipilimumab) INDICATION & IMPORTANT SAFETY INFORMATION

Gervoy (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 immun-mediated reactions.

Recommended Dose Modifications

Withhold dose for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy
Immune-mediated Dermatitis:

- 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

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

There were 63 (12%) YERVOY-treated patients with moderate (Grade 2) immune-mediated 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, angioathy, 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.

Immun-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 advances in a rapidly evolving 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. This includes conducting research on the potential of combining immuno-oncology agents that target different and complementary 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 clinical trials of Yervoy for the investigational uses described in this release will support regulatory filings, or that the investigational uses of Yervoy described in this release will lead to additional approved indications, or, if approved, that they will become commercially successful. 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, 2013 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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