Bristol-Myers Squibb and MD Anderson Cancer Center Announce Novel Research Collaboration in Immuno-Oncology Focused on Leukemia and Hematologic Malignancies

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HOUSTON & NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) and The University of Texas MD Anderson Cancer Center today announced a novel clinical research collaboration to evaluate multiple immunotherapies, including Opdivo (nivolumab), Yervoy (ipilimumab) and three early-stage clinical immuno-oncology assets from Bristol-Myers Squibb, as potential treatment options for acute and chronic leukemia as well as other hematologic malignancies.

The agreement represents an innovative approach to research by focusing numerous clinical trials using multiple agents, in mono and combination regimens, on a specific disease target, in this case select hematologic malignancies. Through this approach, Bristol-Myers Squibb and MD Anderson aim to benefit patients by expediting the delivery of new therapies. The collaboration will launch up to 10 phase 1 and 2 clinical trials, conducted by MD Anderson, focused on evaluating investigational immune-based approaches for acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) and myelofibrosis (MF). Additional studies will be determined by the collaboration at a later date.

Opdivo (nivolumab) is an investigational PD-1 immune checkpoint inhibitor currently approved in Japan for the treatment of patients with unresectable melanoma, and Yervoy (ipilimumab) is a CTLA-4 immune checkpoint inhibitor approved in the U.S. and more than 40 countries for patients with unresectable or metastatic melanoma. Bristol-Myers Squibb has proposed the name Opdivo (pronounced op-dee-voh), which, if approved by health authorities, will serve as the trademark for nivolumab.

“Collaborations between industry and academia can offer a faster and broader spectrum of clinical trials to benefit patients,” said Hagop Kantarjian, M.D., chair of leukemia at MD Anderson. “We hope innovative collaborations such as this can help lead to a higher likelihood for success across the board and will speed up the clinical development of new compounds for delivery to the patients who need them.”

“Immunotherapy is an extremely promising area of research and a key area of focus for MD Anderson’s Moonshots Program,” said MD Anderson President Ron DePinho, M.D. “Partnerships between academia and industry have the potential to significantly advance the application of new discoveries to cancer treatment.”

“Bristol-Myers Squibb is committed to advancing the field of immuno-oncology and complementing our broad research and discovery programs through innovative collaborations with partners who share our commitment to patients,” said Francis Cuss, MB BChir, FRCP, executive vice president and chief scientific officer, Bristol-Myers Squibb. “Cooperation between industry and academia offers a tremendous opportunity to strengthen our scientific and clinical understanding of the role of the immune system in treating cancer.”

Immunooncology is an innovative approach to cancer research and treatment that is designed to harness the body’s own immune system to fight cancer. Hematologic malignancies represent significant areas of high unmet need marked by poor outcomes among the elderly, high-risk patients and for those with multiple relapses. Existing clinical research, including studies by MD Anderson, support further research into the potential of immunotherapies as treatment options for leukemia and other hematologic malignancies.

About Opdivo (nivolumab)

Cancer cells may exploit “regulatory” pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack. Opdivo is an investigational, fully-human PD-1 immune checkpoint inhibitor that binds to the checkpoint receptor PD-1 (programmed death-1) expressed on activated T-cells.

Bristol-Myers Squibb has a broad, global development program to study Opdivo in multiple tumor types consisting of more than 35 trials – as monotherapy or in combination with other therapies – in which more than 7,000 patients have been enrolled worldwide. Among these are several potentially registrational trials in non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), head and neck cancer, glioblastoma and non-Hodgkin lymphoma.

In 2013, the FDA granted Fast Track designation for Opdivo in NSCLC, melanoma and RCC. In April 2014, the company initiated a rolling submission with the FDA for Opdivo in third-line pre-treated squamous cell NSCLC and expects to complete the submission by year-end. The FDA granted its first Breakthrough Therapy Designation for Opdivo in May 2014 for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab. On July 4, Ono Pharmaceutical Co. announced that Opdivo received manufacturing and marketing approval in Japan for the treatment
of patients with unresectable melanoma, making *Opdivo* the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. On September 26, Bristol-Myers Squibb announced that the FDA accepted for priority review the Biologics License Application (BLA) for previously treated advanced melanoma, and the Prescription Drug User Fee Act (PDUFA) goal date for a decision is March 30, 2015. The FDA also granted *Opdivo* Breakthrough Therapy status for this indication. In the European Union, the European Medicines Agency (EMA) has validated for review the Marketing Authorization Application (MAA) for *Opdivo* in advanced melanoma. The application has also been granted accelerated assessment by the EMA’s Committee for Medicinal Products for Human Use (CHMP). The EMA also validated for review the MAA for nivolumab in NSCLC.

**About Yervoy (ipilimumab)**

*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, including Taiwan. 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.

**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 advances in the innovative field of 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 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.

**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 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 19 (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, angioopathy, 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 www.bms.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, please visit www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

About MD Anderson

The University of Texas MD Anderson Cancer Center in Houston ranks as one of the world’s most respected centers focused on cancer patient care, research, and education and prevention. MD Anderson is one of only 41 comprehensive cancer centers
designated by the National Cancer Institute (NCI). For the past 25 years, MD Anderson has ranked as one of the nation’s top two cancer centers in U.S. News & World Report’s annual “Best Hospitals” survey. MD Anderson receives a cancer center support grant from the NCI of the National Institutes of Health (P30 CA016672).

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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 immunotherapies discussed in this release will be successfully developed or approved for any of the indications described in this release, such as acute and chronic leukemia and other hematologic malignancies. 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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