Bristol-Myers Squibb and Ono Pharmaceutical Co., Ltd. Announce Strategic Immuno-Oncology Collaboration in Japan, South Korea and Taiwan

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Companies to develop and commercialize Opdivo (nivolumab), Yervoy (ipilimumab), and three early-stage clinical immuno-oncology assets as single agents and combination regimens

Bristol-Myers Squibb gains access to Opdivo in Japan, South Korea and Taiwan, broadening company’s leadership in immuno-oncology

Ono strengthens its immuno-oncology portfolio with access to additional assets

Collaboration will leverage global clinical trials by including patients from Japan, South Korea and Taiwan

NEW YORK & OSAKA, Japan--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) and Ono Pharmaceutical Co., Ltd. (“Ono”) have signed a strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies as single agents and combination regimens to help address the unmet medical needs of patients with cancer in Japan, South Korea and Taiwan. As part of the agreement, Bristol-Myers Squibb and Ono will jointly develop and commercialize Opdivo (nivolumab) and Yervoy (ipilimumab) across a broad range of tumor types.

Opdivo is a PD-1 immune checkpoint inhibitor approved in Japan for the treatment of patients with unresectable melanoma, making it the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world, and is being developed in multiple tumor types in more than 35 clinical trials. Yervoy, a CTLA-4 immune checkpoint inhibitor, is approved in Taiwan for the treatment of patients with advanced melanoma who have received prior therapy, and is in late-stage development as a potential treatment option for melanoma, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) in Japan. The agreement includes three additional early-stage clinical immuno-oncology assets from Bristol-Myers Squibb: lirilumab, an antibody that blocks the KIR receptor on natural killer cells, urelumab, an agonist of the CD137 co-stimulatory receptor, and BMS-986016, a LAG3 immune checkpoint inhibitor.

Bristol-Myers Squibb and Ono will jointly pursue development of monotherapy and combination regimens, with Opdivo as the foundational therapy in Japan, South Korea and Taiwan, and leverage global clinical trials by including patients from the three countries.

“Bristol-Myers Squibb’s collaboration with Ono supports our goal to maximize the full potential of our immuno-oncology portfolio for patients worldwide,” said Lamberto Andreotti, chief executive officer, Bristol-Myers Squibb. “This collaboration combines our leadership in immuno-oncology with both companies’ experience and capabilities in Asia, and strengthens our long-standing relationship with Ono.”

“Our collaboration with Bristol-Myers Squibb strengthens our ability to further enhance the potential of Opdivo, for which Ono recently received manufacturing and marketing approval in Japan as the first PD-1 inhibitor approved anywhere in the world,” said Gyo Sagara, President, Representative Director and CEO, Ono. “By pursuing the study of investigational combination regimens of immunotherapies with Bristol-Myers Squibb, we hope to bring a range of new therapeutic options to cancer patients.”

Under the terms of the agreement, Bristol-Myers Squibb and Ono will jointly develop and commercialize all collaboration products in Japan, South Korea and Taiwan. Development costs and commercial profits will be shared equally when Opdivo is used in combination with any Bristol-Myers Squibb compound (Yervoy, lirilumab, urelumab, BMS-986016). For a Bristol-Myers Squibb compound used as monotherapy, or two Bristol-Myers Squibb compounds used in a combination regimen, Bristol-
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
Immune-mediated Neuropathies:

- 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 occurred in 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 Guillaín-Barré–like syndromes

- Initiate 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 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 thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland
- Withhold Yervoy in symptomatic patients. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. Long-term hormone replacement therapy may be necessary

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations:

- In the pivotal Phase 3 study in Yervoy-treated patients, clinically significant immune-mediated adverse reactions seen in <1% were: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia
- Across the clinical development program for Yervoy, likely immune-mediated adverse reactions also reported with <1% incidence were: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, and ocular myositis
- Permanently discontinue Yervoy for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions
- Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue Yervoy for immune-mediated ocular disease unresponsive to local immunosuppressive therapy

Pregnancy & Nursing:

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

Common Adverse Reactions:

- The most common adverse reactions (≥5%) in patients who received Yervoy at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%)

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

Immu-No-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.

About the Bristol-Myers Squibb and Ono Collaboration

Bristol-Myers Squibb, through its wholly owned subsidiary Medarex, Inc., and Ono have a long-standing relationship since 2005 to develop and commercialize PD-1 antibodies, including Opdivo. Bristol-Myers Squibb obtained rights to develop and commercialize Opdivo in North America in 2009 as part of the Medarex, Inc. acquisition. Through a collaboration agreement entered into in September 2011, Ono granted Bristol-Myers Squibb exclusive rights to develop and commercialize Opdivo in the rest of the world, except in Japan, South Korea and Taiwan where Ono retained such rights.

On July 23, 2014, Bristol-Myers Squibb and Ono signed a new collaboration agreement in which the companies agreed to jointly develop and commercialize Opdivo, Yervoy and three early-stage immunotherapies in Japan, South Korea and Taiwan.

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 Ono Pharmaceutical Co., Ltd.

Ono Pharmaceutical Co., Ltd., headquartered in Osaka, Japan, is an R&D-oriented pharmaceutical company committed to creating innovative medicines in specific areas. It focuses especially on the diabetes and oncology areas. For more information, please visit the company’s website at http://www.ono.co.jp/eng/index.html.

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 any of the compounds mentioned in this release will receive regulatory approval in Japan, South Korea or Taiwan, either as single agents (other than Yervoy in Taiwan and Opdivo in Japan) or in combination regimens, or, if approved, that they will become commercially successful products. 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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