One- & Two-Year Survival Rates of 94% and 88% Announced from Phase 1b Trial of Investigational PD-1 Checkpoint Inhibitor Nivolumab and Yervoy® (ipilimumab) in Advanced Melanoma; Ongoing Phase 2/3 Trials to Confirm Results

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PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced follow up results from Study -004, a multi-arm Phase 1b dose-ranging trial evaluating the safety and activity of the combination regimen of nivolumab, an investigational PD-1 immune checkpoint inhibitor, and Yervoy® (ipilimumab) given either concurrently or sequentially in patients with advanced melanoma (n=127). After an additional year of follow up of the cohort that received the concurrent combination regimen of nivolumab 1 mg/kg plus Yervoy 3mg/kg (n=17), the one-year overall survival (OS) rate was 94% and the two-year OS rate was 88%. These are the doses used in the ongoing Phase 2 and Phase 3 trials, CheckMate -069 and -067. No new safety signals were reported in the concurrent combination cohorts with additional follow up (n=53) and grade 3-4 treatment-related adverse events (AEs) occurred in 62% of patients. The most common were asymptomatic increases in lipase (15%), ALT (12%) and AST (11%). These data will be presented today at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) and featured during an ASCO press briefing at 8 a.m. CDT (Abstract # LBA9003).

“The treatment of advanced melanoma has changed dramatically in the last few years, but there continues to be a need to increase the number of patients who experience a long-term survival benefit,” said Dr. Mario Sznol, Yale University School of Medicine and Yale Cancer Center, presenter of the results. “While these are Phase 1b data, the duration of response and one- and two-year survival rates observed with the combination regimen of nivolumab and Yervoy are very encouraging and support the rationale for the ongoing, late stage trials of this combination regimen.”

“The science of immuno-oncology - harnessing the patient’s immune system to treat cancer - is rapidly evolving,” said Michael Giordano, senior vice president, Head of Development, Oncology & Immunology at Bristol-Myers Squibb. “These results are the most advanced data set to date evaluating the potential of combining immune checkpoint inhibitors. As leaders in the field, they reinforce our aspiration that combining immunotherapies may be foundational and may have the potential to change the standard of care by transforming survival expectations.”

Results from Phase 1b Combination Regimen (Study -004)

Study 004 is a dose-ranging Phase 1 study (n=127) evaluating the safety, antitumor activity and pharmacokinetics of the combination regimen of nivolumab and Yervoy given concurrently or sequentially in patients with advanced melanoma. Prior to enrollment, patients could have received up to three systemic therapies.

In the concurrent regimen cohort (n=53), eligible patients received nivolumab and Yervoy every three weeks for four doses, followed by nivolumab alone every three weeks for four doses. This concurrent combination regimen treatment was subsequently continued every 12 weeks for up to eight doses. Cohorts of a maximum of 17 patients per dose level were enrolled (nivolumab 0.3 mg/kg + Yervoy 3 mg/kg [n=14]; nivolumab 1 mg/kg + Yervoy 3 mg/kg [n=17]; nivolumab 3 mg/kg + Yervoy at an investigational dose of 1 mg/kg [n=16]; nivolumab 3 mg/kg + Yervoy 3 mg/kg [n=6]). In an expansion cohort (n=41), eligible patients received the concurrent combination regimen of nivolumab 1 mg/kg and Yervoy 3 mg/kg every three weeks for four doses, followed by nivolumab alone at 3 mg/kg every two weeks until progression, which is the same schedule utilized in the ongoing Phase 2 and Phase 3 trials. In the sequenced regimen cohort (n=33), patients previously treated with Yervoy received nivolumab alone at 1 mg/kg or 3 mg/kg every two weeks.

Results from this trial were first published in the New England Journal of Medicine and presented at ASCO in 2013. The updated data, including those shown below, are based on a median follow up of 22 months and reflect an additional year of follow up from patients initially enrolled in the trial.

Efficacy Summary: Concurrent and Sequenced Cohorts

<table>
<thead>
<tr>
<th>Nivolumab (mg/kg) + Yervoy (mg/kg) [n]</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>1-Year OS, %</th>
<th>2-Year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent Cohorts [53]</td>
<td>42</td>
<td>17</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>0.3 + 3 [14]</td>
<td>21</td>
<td>14</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>1 + 3 [17]</td>
<td>53</td>
<td>18</td>
<td>94</td>
<td>88</td>
</tr>
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</table>
Responses were observed regardless of BRAF mutational status or PD-L1 expression.

No new safety signals were reported with additional follow up. Grade 3-4 treatment-related AEs occurred in 62% of patients in the concurrent cohorts, managed with standard algorithms. The most common were asymptomatic increases in lipase (15%), ALT (12%) and AST (11%). Twenty-two patients (23%) discontinued treatment due to related AEs. There was one drug-related death due to fatal multi-organ failure following an initial event of colitis.

About Advanced Melanoma

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin. Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to other organs, such as the lymph nodes, lungs, brain or other areas of the body. The incidence of melanoma has been increasing for at least 30 years. In 2012, an estimated 232,130 melanoma cases were diagnosed globally. Melanoma is mostly curable when treated in its early stages. However, in its late stages, the average survival rate has historically been just six months with a one-year mortality rate of 75%, making it one of the most aggressive forms of cancer.

About Bristol-Myers Squibb Immuno-Oncology Trials in Melanoma

Bristol-Myers Squibb is committed to the research and development of immuno-oncology as an innovative approach to treating melanoma and has a broad development program evaluating its approved and investigational immunotherapies – either as single agents or as part of a regimen - across lines of therapy, stages of disease and biomarker expression. Among these are five Phase 3 trials. There are two ongoing Phase 3 trials evaluating nivolumab as a single agent at the 3 mg/kg dose in treatment-naive patients (CheckMate -066) as well as in patients who have been previously treated (CheckMate -037). A Phase 3 trial evaluating Yervoy 3 mg/kg vs. Yervoy 10 mg/kg in patients with previously treated or treatment-naive metastatic melanoma is ongoing (Study -169) and the first results of a Phase 3 trial evaluating the investigational use of Yervoy 10 mg/kg in patients with Stage 3 melanoma who are at high risk of recurrence following complete surgical resection (Study -029) will be featured today during an ASCO press briefing at 8 a.m. CDT and presented in an oral session at 3 p.m. CDT (Abstract #LBA9008). Additionally, a Phase 3 trial evaluating the combination regimen of nivolumab and Yervoy in treatment-naive patients is ongoing (CheckMate -067).

About Nivolumab and Yervoy

Cancer cells may exploit “regulatory” pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack. Nivolumab and Yervoy are both monoclonal antibodies and immune checkpoint inhibitors, but target different receptors for distinct T-cell checkpoint pathways.

Nivolumab 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. We are investigating whether by blocking this pathway, nivolumab would enable the immune system to resume its ability to recognize, attack and destroy cancer cells.

Bristol-Myers Squibb has a broad, global development program to study nivolumab 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 nivolumab in NSCLC, melanoma and RCC. Earlier this month, the FDA granted nivolumab Breakthrough Therapy Designation for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab.

Yervoy, which is a recombinant, human monoclonal antibody, blocks the cytotoxic T- lymphocyte antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab 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 ipilimumab’s effect in patients with melanoma is indirect 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.

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 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

• 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 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, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, biephalitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiform, scleroderma, 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.

**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 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 the Bristol-Myers Squibb and Ono Pharmaceutical Partnership**

Through a collaboration agreement with Ono Pharmaceutical in 2011, Bristol-Myers Squibb expanded its territorial rights to develop and commercialize nivolumab (BMS-936558/ONO-4538) globally except in Japan, Korea and Taiwan where Ono has retained all rights to the compound.

**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](http://www.bms.com) or follow us on Twitter at [http://twitter.com/bmsnews](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 product development. 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 nivolumab will receive regulatory approval, that the combination use of nivolumab and Yervoy will receive regulatory approval, or that, if approved, 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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English

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