Investigational PD-1 Immune Checkpoint Inhibitor Nivolumab Showed Antitumor Activity in Previously Treated and Chemotherapy-Naïve Patients in Phase 1b Non-Small Cell Lung Cancer Trials

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- Longer-term data from study of previously treated patients who received nivolumab as a single agent showed a two-year survival rate of 24% across doses; results from 3 mg/kg dose also presented (Study -003)
- In chemotherapy-naïve patients who received nivolumab 3 mg/kg as a single agent, the overall response rate (ORR) was 50% in PD-L1 positive tumors and 0% in PD-L1 negative tumors (CheckMate - 012)
- The types of treatment-related serious adverse events (SAEs) in CheckMate -012 were consistent with those in other nivolumab trials; of the chemotherapy-naïve patients who received nivolumab as a single agent, 15% experienced grade 3-4 treatment-related SAEs

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced results from a Phase 1b study evaluating the safety and efficacy of its investigational PD-1 immune checkpoint inhibitor nivolumab as a single agent in patients with advanced non-small cell lung cancer (NSCLC) who were previously treated (Study -003) and a Phase 1b study evaluating nivolumab as a single agent in chemotherapy-naïve patients (CheckMate -012). In Study -003, the two-year survival rate was 24% across doses (n=129) for previously-treated patients who received nivolumab as a single agent and highest at 45% in patients who received the 3 mg/kg dose (n=37). In CheckMate -012, the overall response rate (ORR) was 50% in PD-L1 positive tumors and 0% in PD-L1 negative tumors for chemotherapy-naïve patients who received nivolumab as a single agent (n=20). The types of treatment-related serious adverse events (SAEs) in CheckMate -012 were consistent with those in other nivolumab trials with 15% of patients experiencing grade 3-4 treatment-related SAEs. These data will be presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) taking place in Chicago May 30-June 3.

“As the leading cause of cancer death, lung cancer remains an area of significant unmet medical need,” said Michael Giordano, senior vice president, Head of Development, Oncology & Immunology. “Bristol-Myers Squibb has the largest clinical development program in the industry evaluating the potential of immuno-oncology compounds in lung cancer as single agents and as part of combination regimens across lines of therapy, histologies and biomarker expression. These Phase 1b data from both previously treated and chemotherapy-naïve patients add to our understanding of the role of PD-L1 expression and reinforce our belief in nivolumab – as a single agent and as part of a combination regimen - as a potential treatment option for patients with lung cancer.”

**Results from Phase 1b Single Agent Study in Previously-Treated Patients (Study -003)**

Study -003 is a Phase 1b dose escalation study (n=306) evaluating the safety, antitumor activity and pharmacokinetics of nivolumab as a single agent in previously-treated patients with advanced melanoma (n=107), NSCLC (n=129), renal cell carcinoma (n=34), castration-resistant prostate cancer (n=17) or colorectal cancer (n=19). Based on an amendment to the protocol, patients were followed for survival. Eligible patients were administered nivolumab as an intravenous infusion every two weeks of each eight-week treatment cycle. Cohorts of three to six patients per dose level (0.1, 0.3, 1.0, 3.0 or 10 mg/kg) were enrolled sequentially. Patients continued treatment ≤2 years (12 cycles), unless they experienced complete response, unacceptable toxicity, progressive disease or withdrew consent.
Efficacy and safety results from this study were initially presented at ASCO and published in the *New England Journal of Medicine* in 2012. Updated results from the lung cancer cohort, including those shown below, will be presented at ASCO on May 31 at 1:15 p.m. CDT (Abstract #8112).

**Long-Term Nivolumab Single Agent Efficacy Data in Previously-Treated NSCLC Patients**

<table>
<thead>
<tr>
<th>Patients</th>
<th>mOS,* mo (95% CI)</th>
<th>OS Rate,* % (95% CI) [Pts at Risk]</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1 Year</td>
<td>2 Year</td>
</tr>
<tr>
<td>All† n=129</td>
<td>9.9 (7.8, 12)</td>
<td>42 (34, 51) [48]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 (16, 32) [20]</td>
</tr>
<tr>
<td>1 mg/kg n=33</td>
<td>9.2 (5.3, 11)</td>
<td>32 (16, 49) [8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (3, 27) [2]</td>
</tr>
<tr>
<td>3 mg/kg n=37</td>
<td>14.9 (7.3, NR)</td>
<td>56 (38, 71) [17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 (27, 61) [9]</td>
</tr>
<tr>
<td>10 mg/kg n=59</td>
<td>9.2 (5.2, 12)</td>
<td>40 (27, 52) [23]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 (10, 31) [9]</td>
</tr>
<tr>
<td>Squamous n=54</td>
<td>9.2 (7.3, 12)</td>
<td>40 (27, 54) [19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 (13, 37) [9]</td>
</tr>
<tr>
<td>Non-squamous n=74</td>
<td>10.1 (5.7, 14)</td>
<td>43 (32, 54) [28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 (13, 34) [10]</td>
</tr>
</tbody>
</table>

NR= not reached. *Sept 2013 analysis. †One pt had unknown histology.

Data to be presented at the 2014 ASCO annual meeting, with all patients having greater than or equal to one year of follow up, demonstrated a spectrum, frequency and severity of treatment-related adverse events (AEs) that were consistent with those initially reported in the study at ASCO in 2012. Common drug-related AEs included fatigue, decreased appetite, diarrhea, nausea, constipation, cough and dyspnea. Drug-related select AEs with potential immunologic etiologies, defined as adverse events that may require more frequent monitoring and/or unique intervention, included rash, diarrhea and pruritus. These data support the ongoing evaluation of nivolumab as a single agent at the 3 mg/kg dose in patients with previously treated advanced NSCLC in the Phase 3 CheckMate -017 and CheckMate -057 studies.

**Results from Phase 1b Study of Chemotherapy-Naïve Patients (CheckMate -012)**

CheckMate -012 is a multi-arm Phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced NSCLC, as either a single agent or as part of a regimen with other agents, including in combination with Yervoy® (ipilimumab), at different doses and schedules. Secondary outcomes include ORR and progression free survival (PFS). Results from patients who received nivolumab as a single agent, including those shown below, will be presented at ASCO on June 3 at 11:30 a.m. CDT (Abstract #8024).

In patients who received nivolumab 3 mg/kg as a single agent (n=20), the objective response rate (ORR) was 50% in patients whose tumors were PD-L1 positive and 0% for tumors that were PD-L1 negative. Responses were observed in both squamous and non-squamous histological subtypes. Median duration of response has not been reach after a median of 15 months of follow up.

**Efficacy Results for Nivolumab Single Agent and by PD-L1 Tumor Status**

<table>
<thead>
<tr>
<th></th>
<th>ORR n/N (%)</th>
<th>mDOR wk (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>6/20 (30)</td>
<td>NR (24+, 71+)</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>5/10 (50)</td>
<td>NR (24+, 71+)</td>
</tr>
<tr>
<td>PD-L1-</td>
<td>0/7 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>PD-L1 unavailable*</td>
<td>1/3 (33)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

NR = Not Reached; *3 of the 20 treated patients had insufficient tumor samples for analysis.

After a median of 15 months of follow up, grade 3/4 treatment-related SAEs were reported in 3 patients (15%) and included AST (5%) or ALT (5%) elevations, cardiac failure and hyperglycemia (5%). No pneumonitis (any grade) was observed. These data support the ongoing evaluation of nivolumab as a single agent at the 3 mg/kg dose in the first-line treatment of advanced NSCLC patients in the Phase 3 CheckMate -026 study.

Preliminary data from a cohort of patients who received the combination regimen of nivolumab and Yervoy at different doses (n=49) will be presented at ASCO on June 3 at 11:30 a.m. CDT (Abstract #8023) and showed activity, as assessed by ORR, in patients with both PD-L1 positive and PD-L1 negative tumors. A Phase 3 trial evaluating the combination regimen of nivolumab and Yervoy in chemotherapy-naïve patients will be initiated by the end of 2014.

Data from additional arms of CheckMate -012, including nivolumab as part of a regimen with chemotherapy doublets and erlotinib, will also be presented at ASCO (Abstract #8113, #8022).
About Lung Cancer
Lung cancer is the leading cause of cancer deaths globally, resulting in more than 1.5 million deaths each year according to the World Health Organization. NSCLC is one of the most common types of the disease and accounts for approximately 85 percent of cases. Survival rates vary depending on the stage and type of the cancer when it is diagnosed. Globally, the five-year survival rate for Stage I NSCLC is between 47 and 50 percent; for Stage IV NSCLC, the five-year survival rate drops to two percent.

About Bristol-Myers Squibb Immuno-Oncology Trials in Lung Cancer
Bristol-Myers Squibb is committed to the research and development of immuno-oncology as an innovative approach to treating lung cancer and has a broad global development program evaluating its approved and investigational immunotherapies – either as single agents or as part of combination regimens - across lines of therapy, histologies and biomarker expression. Among these are six ongoing Phase 3 trials. Three Phase 3 trials are evaluating nivolumab as a single agent in patients who have been previously treated (CheckMate -017 and CheckMate -057) as well as chemotherapy-naive patients (CheckMate -026). Two Phase 3 trials evaluating Yervoy in combination with chemotherapy in newly diagnosed small cell lung cancer (Study -156) and squamous NSCLC (Study -104) are ongoing. Additionally, the company plans to initiate a Phase 3 trial evaluating the combination regimen of nivolumab and Yervoy in chemotherapy-naive patients with advanced NSCLC by the end of 2014.

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 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.

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...
in 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 immunemediated 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 necrosis
  - 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:**
YERVOY® is a registered trademark of Bristol-Myers Squibb Company.

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.
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 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 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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