Bristol-Myers Squibb Announces Long-Term Survival Results from Pooled Analysis of Yervoy® (ipilimumab) Treatment in More Than 1,800 Patients with Metastatic or Locally Advanced or Unresectable Melanoma

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- In this pooled analysis of 12 studies, a plateau in the survival curve begins at approximately three years, with some patients followed for up to ten years
- Three-year estimated survival rate of 22% observed in patients treated with Yervoy
- Findings based on different doses and regimens and show consistency of long-term survival data for Yervoy in metastatic melanoma
- Data presented as a late-breaker at the 2013 European Cancer Congress and highlighted at Congress press briefing

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced results from a pooled analysis of survival data for 12 studies (n=1,861) in patients with metastatic or locally advanced or unresectable melanoma who were treated with Yervoy® (ipilimumab) at different doses and regimens. A plateau in the survival curve begins at approximately three years, with follow-up of up to ten years in some patients. Approximately 22% of patients were alive at three years. The data will be presented at the 2013 European Cancer Congress on September 28 at 1:00 p.m. CEST and were highlighted at a Congress press briefing (Abstract # 24LBA, “Pooled analysis of long-term survival data from Phase 2 and Phase 3 trials of ipilimumab in metastatic or locally advanced, unresectable melanoma”).

Safety data were not included in this analysis. However, safety data from these individual studies have been reported. Overall, the types of adverse events (AEs) attributed to Yervoy are generally mechanism (immune)-based. Yervoy can result in severe and fatal immune-related adverse reactions due to T-cell activation and proliferation. In these clinical trials, adverse events associated with Yervoy were managed with protocol-specific guidelines, including the administration of systemic corticosteroids, dose interruption/discontinuation and/or other immunosuppressants.

“This pooled analysis reinforces the long-term survival data seen in the individual studies and provides additional insight into the overall survival of metastatic melanoma patients treated with Yervoy,” said Brian Daniels, senior vice president, Global Development and Medical Affairs. “The durability and consistency of long-term survival observed in this analysis is encouraging as we continue to advance the research and development of our immuno-oncology portfolio.”

“In this analysis, approximately 26% of treatment-naïve and 20% of previously-treated patients were alive at three years after being treated with an ipilimumab regimen,” said F. Stephen Hodi, M.D., Department of Medicine, Harvard Medical School, Dana-Farber Cancer Institute. “This pooled analysis is encouraging, particularly when considering that metastatic melanoma is one of the most aggressive forms of cancer and historically, average survival was just six to nine months.”

About The Analysis

This pooled analysis was conducted to provide a more precise estimate of the long-term survival effect of Yervoy in patients with metastatic melanoma. It is comprised of patient-level data from 12 prospective and retrospective studies, including two Phase 3 trials (n=790), eight Phase 2 trials (n=821), and two retrospective, observational studies (n=250), which have been or will be reported on as individual studies. Three studies included overall survival follow-up in some patients for up to ten years.

The analysis included both previously-treated (n=1,257) and previously untreated patients (n=604) who received Yervoy at
different doses and regimens. The majority of patients received Yervoy 3 mg/kg (n=965) or 10 mg/kg (n=706). Yervoy was given every 3 weeks for 4 doses, and most studies included the option to receive either Yervoy retreatment or Yervoy maintenance therapy for eligible patients.

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.

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 corticosteroid therapy 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 (ipilimumab)-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 (ipilimumab) 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 severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >2.5x but ≤5x the ULN or total bilirubin elevation >1.5x but ≤3x the ULN; 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) hepatotoxicity
- 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 (ipilimumab) 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 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 severe 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 (ipilimumab) 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, 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 (ipilimumab)-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 hypo-thyroidism
  - 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 (ipilimumab) 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.

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.

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