



Bristol-Myers Squibb Reports Results for Phase 3 Trial of Yervoy® (Ipilimumab) in Previously-Treated Castration-Resistant Prostate Cancer

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Primary endpoint of overall survival did not reach statistical significance in this advanced patient population ($p=0.053$); however, anti-tumor activity was observed in other efficacy endpoints, including progression-free survival

Drug-related adverse events were mostly immune-related, consistent with those observed previously with Yervoy

Phase 3 trial (Study 095) assessing overall survival of Yervoy in patients with less advanced castration-resistant prostate cancer who have received no prior cytotoxic treatment is ongoing

PRINCETON, N.J.--(BUSINESS WIRE)--Sep. 12, 2013-- [Bristol-Myers Squibb Company](#) (NYSE:BMJ) today reported results from the Phase 3 randomized, double-blind clinical trial (Study 043) comparing Yervoy 10 mg/kg (ipilimumab) (n=399) to placebo (n=400) following radiation in patients with advanced metastatic castration-resistant prostate cancer (mCRPC) who have received prior treatment with docetaxel. The study's primary endpoint of overall survival (OS) did not reach statistical significance (HR = 0.85; 95% CI = 0.72-1.00; $p = 0.053$). However, anti-tumor activity was observed across some efficacy endpoints, including progression free-survival. These data will be presented at the 2013 European Cancer Congress in an oral session on September 28 (Abstract # 2850).

Treatment-related adverse events were common, with most being immune-related (irAEs), and were managed using standard Yervoy management protocols. Grade ≥ 3 irAEs in the Yervoy and placebo arms, respectively, were gastrointestinal (GI; 18% vs. 1%), liver (5% vs. 1%), endocrine (2% vs. 1%), and dermatologic (1% vs. 0%). The incidence of drug-related death was 1%.

"While we are disappointed that the primary endpoint of overall survival was not met, we remain encouraged that results in this advanced population support the potential role of immunotherapies for prostate cancer. We are committed to continuing our development of Yervoy in prostate cancer," said [Brian Daniels](#), senior vice president, Global Development and Medical Affairs, Bristol-Myers Squibb. "Immuno-oncology is a rapidly evolving treatment modality and findings from this study provide important scientific insights that can be applied to current and future studies of Yervoy as well as our broad pipeline of immunotherapies in development."

Yervoy 3 mg/kg monotherapy is currently approved in more than 40 countries for the treatment of patients with unresectable or metastatic melanoma.

"Although the study did not meet its primary endpoint, clinical activity was observed in this Phase 3 trial with a suggestion of greater activity in those with less advanced castration-resistant prostate cancer," said [W.R. Gerritsen](#), MD, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands. "These results offer important insights for ongoing and future studies of Yervoy in prostate cancer, including a second large trial of Yervoy in patients with less advanced disease."

The Phase 3 program for Yervoy includes Study 095, an ongoing Phase 3 randomized double-blind trial comparing the efficacy of Yervoy 10 mg/kg versus placebo in patients with mCRPC who have not received prior cytotoxic treatment. Yervoy is also being studied in Phase 3 trials in adjuvant melanoma and non-small cell lung cancer.

Study 043 Results

In the intent-to-treat population, the median OS was 11.2 months for Yervoy and 10 months for placebo and the hazard ratio was 0.85 (95% CI = 0.72-1.00; $p = 0.053$). The one- and two-year survival rates for Yervoy versus placebo were 47% versus 40%, and 26% versus 15%, respectively.

Median progression-free survival favored Yervoy over placebo (HR=0.70; 95% CI = 0.61-0.82) as did prostate-specific antigen (PSA) response rates, as evidenced by declines of $\geq 50\%$ in evaluable patients (13.1% vs. 5.3%, respectively). Pre-specified subset analyses suggest that Yervoy may be more active in patients with indicators for less advanced disease.

Treatment-related adverse events were common and most were immune-related. Grade ≥ 3 irAEs in the Yervoy and placebo arms, respectively, were gastrointestinal (GI; 18% vs. 1%), liver (5% vs. 1%), endocrine (2% vs. 1%), and dermatologic (1% vs. 0%). Most were managed using standard Yervoy management protocols, including the administration of systemic corticosteroids, dose interruption/discontinuation and/or other immunosuppressants. Incidences of drug-related death and GI perforation, per investigator assessment, were 1% and 0.5%, respectively.

About Study 043

CA-184-043 is a randomized, double-blind, Phase 3 study comparing Yervoy to placebo following radiotherapy in patients with CRPC who have received prior treatment with docetaxel. Patients received bone-directed radiation therapy after being randomly assigned 1:1 to receive Yervoy 10 mg/kg (n=399) or placebo (n=400) every three weeks for a total of four doses. Eligible patients received maintenance treatment every three months.

Patient baseline characteristics were indicative of advanced disease. Forty-eight percent had baseline pain of ≥ 4 , based on the Brief Pain Inventory (BPI), a questionnaire used by clinicians to assess and measure pain.

About Prostate Cancer

Prostate cancer is the second most frequently diagnosed cancer and the sixth most deadly cancer in men. In the United States, it is estimated that more than 238,000 men will be diagnosed with prostate cancer and more than 29,700 will die from the disease in 2013. Most of these deaths will be caused by metastatic castration-resistant prostate cancer, which occurs when the cancer becomes resistant to standard hormonal treatment and spreads from the prostate to other organs in the body. New treatment options have recently become available for patients with mCRPC, yet the disease remains largely incurable.

About Yervoy

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. 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 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) INDICATIONS & IMPORTANT SAFETY INFORMATION

YERVOY 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 $>5 \times$ the upper limit of normal (ULN) or total bilirubin $>3 \times$ 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 \leq 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

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 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, 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, and autoimmune thyroiditis

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

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