New Data Demonstrate Significant Improvement in Progression-Free Survival for Triple Negative Metastatic Breast Cancer Patients Treated with IXEMPRA™ Plus Capecitabine

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SAN ANTONIO--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced new data from studies of IXEMPRA™ (ixabepilone) plus capecitabine compared to capecitabine alone, including a pre-specified sub set analysis demonstrating a significant increase in progression free survival (PFS) in patients with triple negative breast cancer.

The study results -- which are from a pooled analysis of approximately 2,000 patients enrolled in two Phase III clinical trials of IXEMPRA (046 and 048) -- were presented today at the 2008 San Antonio Breast Cancer Symposium (SABCS). Patients studied were either resistant to or pretreated with anthracyclines and taxanes. In the pooled analysis of the subset of 443 patients with triple negative breast cancer, data show that IXEMPRA plus capecitabine (n = 191 patients) is the first combination regimen to demonstrate statistically significant (p<0.0001) PFS compared to capecitabine (n = 208 patients) alone.

Triple negative breast cancer patients are diagnosed based upon the lack of three “receptors” — estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2). Triple negative tumors are typically aggressive tumors that do not respond to hormonal treatment or HER2 agents and have a faster rate of relapse. Patients with triple negative breast cancer have a shorter overall survival after treatment with traditional chemotherapies.

“Patients with advanced, triple negative breast cancer have limited treatment options and a poor prognosis,” said Hope S. Rugo, M.D., Clinical Professor of Medicine and Director, Breast Oncology Clinical Trials Program, University of California San Francisco Helen Diller Family Comprehensive Cancer Center. "For this reason, it is important to explore the potential of other current and developmental therapies to discover more and effective treatment options for patients with this specific type of breast cancer.”

In the triple negative pooled subset analysis, patients who received IXEMPRA and capecitabine had an overall response rate (ORR) of 31 percent compared to 15 percent for patients who received capecitabine alone. The PFS of the combination group was a median of 4.2 months compared to a median of 1.7 months (Hazard Ratio 0.63, 95% CI: 0.52-0.77) for the capecitabine-treated group. Both results were statistically significant. Although improvement in overall survival was noted, the pooled analysis did not demonstrate statistical significance.

IXEMPRA (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death. The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA were peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthritis, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional reactions occurred in ≥20% in combination treatment: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation. Drug-associated hematologic abnormalities (≥40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

In addition to the study in triple negative patients, other pooled data analyses from studies 046 and 048 were presented at SABCS, including data on patients with taxane resistance, patients who had relapsed 12 months or less after adjuvant treatment with an anthracycline and a taxane and symptomatic patients who had Kameofsky performance status of 70-80.

About IXEMPRA Studies 046 and 048

The Phase III studies -- 046 and 048 used for the pooled analysis -- included patients with metastatic or locally advanced breast cancer whose disease had been treated with two widely used and approved chemotherapies (anthracycline and taxane). In study 046 patients were resistant to these therapies. The primary endpoint for this study was PFS and secondary endpoint was overall survival. In study 048 patients were pretreated with anthracyclines and taxanes. The primary endpoint for 048 was overall survival and the secondary endpoint was progression free survival. Although improvement in overall survival was noted, both studies did not demonstrate statistical significance. Progression free survival for both studies were statistically significant.

About IXEMPRA™

IXEMPRA™, is an epothilone approved as monotherapy for the treatment of patients with metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine. IXEMPRA is also approved in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast
cancer resistant to treatment with an anthracycline, and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within six months in the adjuvant setting or three months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or four months in the metastatic setting.

**IMPORTANT SAFETY INFORMATION**

**Toxicity in Hepatic Impairment**

IXEMPRA (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death.

In combination with capecitabine, the overall frequency of Grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity related deaths was greater in patients with hepatic impairment.

Caution should be used when using IXEMPRA as monotherapy in patients with AST or ALT > 10 x ULN or bilirubin >3 x ULN is not recommended.

With monotherapy, Grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment.

**Contraindications**

IXEMPRA is contraindicated in patients:

- with a known history of a severe (CTC Grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives such as polyoxyethylated castor oil.
- who have a baseline neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³.

**Peripheral Neuropathy**

Peripheral neuropathy was common. Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. Neuropathy occurred early during treatment; approximately 75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA. Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or existing moderate to severe neuropathy.

**Myelosuppression**

Myelosuppression is dose-dependent and primarily manifested as neutropenia. Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA.

Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced. Neutropenia-related deaths occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine. Neutropenia-related death occurred in 0.4% of 240 patients with IXEMPRA as monotherapy.

**Hypersensitivity Reaction**

Premedicate with an H₁ and an H₂ antagonist approximately 1 hour before IXEMPRA infusion and observe for hypersensitivity reactions (e.g., flushing, rash, dyspnea, and bronchospasm).

In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (e.g., epinephrine, corticosteroids) started.

Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H₁ and H₂ antagonists, and extension of the infusion time should be considered.

**Pregnancy**

Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus.

**Cardiac Adverse Reactions**

Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (e.g., myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group.

**Potential for Cognitive Impairment from Excipients**

IXEMPRA contains dehydrated alcohol USP. Consideration should be given to the possibility of central nervous system and other effects of alcohol.

**Adverse Reactions**

**Monotherapy** - The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA monotherapy were peripheral sensory neuropathy, 62% (grade 3/4: 14%); fatigue/asthenia, 56% (grade 3/4: 13%); myalgia/arthralgia, 49% (grade
Combination with capecitabine - The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA in combination with capecitabine compared to capecitabine alone, respectively, were peripheral sensory neuropathy, 65% vs. 16% (grade 3/4 21% vs. 0%); palmar-plantar erythrodysesthesia (hand-foot) syndrome, 64% vs. 63% (grade 3/4 18% vs. 17%); fatigue/asthenia, 60% vs. 29% (grade 3/4 16% vs. 4%); nausea, 53% vs. 40% (grade 3/4 3% vs. 2%); diarrhea, 44% vs. 39% (grade 3/4 6% vs. 9%); vomiting, 39% vs. 24% (grade 3/4 4% vs. 2%); myalgia/arthritis, 39% vs. 5% (grade 3/4 8% vs. <1%); anorexia, 34% vs. 15% (grade 3/4 3% vs. 1%); stomatitis/mucositis, 31% vs. 20% (grade 3/4 4% vs. 3%); alopecia, 31% vs. 3% (grade 3/4 0% vs. 0%); abdominal pain, 24% vs. 14% (grade 3/4 2% vs. 1%); nail disorder, 24% vs. 10% (grade 3/4 2% vs. <1%); musculoskeletal pain, 23% vs. 5% (grade 3/4 2% vs. 0%); and constipation, 22% vs. 6% (grade 3/4 0% vs. <1%). Drug-associated hematologic abnormalities (>40%) included neutropenia, leukopenia, anemia, and thrombocytopenia. Grade 3/4 hematologic adverse reactions included neutropenia, 54%; leukopenia, 49%; anemia, 8%; and thrombocytopenia, 7%.

Please see accompanying full Prescribing Information including boxed WARNING regarding hepatic impairment, or visit www.IXEMPRA.com.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; CTC = common terminology criteria.

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About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to extend and enhance human life.


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