SPRYCEL® (Dasatinib) Shows Potential as Treatment for Prostate Cancer

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Phase II Data to Be Presented at ASCO

NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced interim results from two Phase II studies of SPRYCEL® (dasatinib) which demonstrate that the medicine may have potential as a treatment for a certain type of advanced prostate cancer.

The data will be presented in totality at the American Society for Clinical Oncology (ASCO) annual meeting to be held May 29 to June 2 in Orlando, Florida.

SPRYCEL is currently indicated for the treatment of adults with resistance or intolerance to prior therapy for chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

The Phase II studies (CA180-085 and CA180-086) to be presented at ASCO focus on SPRYCEL's potential as a treatment for castrate-resistant prostate cancer (CRPC). Data from these studies support the rationale for the ongoing global Phase III study (CA180-227) of men with CRPC treated with the combination of SPRYCEL and the current standard of care docetaxel. This ongoing Phase III study is currently recruiting patients in the United States, Mexico, Australia, Canada, South Africa and countries in Europe, Asia and South America. Additional information about the study is available at www.clinicaltrials.gov.

“These preliminary results are promising as we continue to fully develop SPRYCEL for a number of life-threatening tumor types,” said David Shapiro, M.D., vice president, Sprycel development team at Bristol-Myers Squibb. “SPRYCEL is the most clinically advanced SRC inhibitor with demonstrated efficacy and safety in patients with solid tumors.”

In a single-agent study (CA180-085) examining three dosing regimens of SPRYCEL in CRPC patients, preliminary clinical activity (tumor and prostate-specific antigen response; decreasing bone turnover) was similar in patients receiving once-daily or twice-daily SPRYCEL schedules. In an add-on study with docetaxel (CA180-086), the combinations were shown to be well tolerated with no drug-drug interactions observed. Further encouraging clinical activity was also reported.

Most common Grade 1 or 2 adverse events in the CRPC studies included fatigue, headache, diarrhea and nausea. Grade 3 or 4 adverse events included asthenia, dyspnea and three cases of pleural effusion.

In preclinical models, SRC and related kinases (SRC family kinases (SFK)) have been identified as central mediators in oncogenic, invasive and bone metastatic processes and are a potential therapeutic target in solid tumors. Given its central role in these processes, SRC kinase inhibition may have the potential for broad therapeutic activity in patients with SRC-dependent cancers.

“Our clinical trial program is focused on tumor types where SRC and SFK play a central role in promoting tumor growth and metastasis,” said Dr. Shapiro. “To effectively treat CRPC, a comprehensive targeted approach is needed that affects both the tumor and the bone microenvironment.”

SPRYCEL INDICATION

SPRYCEL is currently indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase myeloid leukemia with resistance or intolerance to prior therapy including imatinib and for the treatment of adults with Philadelphia chromosome- positive acute lymphoblastic leukemia (Ph+ ALL) with resistance and intolerance to prior treatment. The effectiveness is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. The currently approved dose for SPRYCEL in chronic phase CML is 100 mg once daily

IMPORTANT SAFETY INFORMATION

Myelosuppression: Treatment with SPRYCEL is associated with severe CTC Grade 3/4 thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in advanced CML or Ph+ALL than in chronic phase CML. Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with preexisting laboratory abnormalities. Complete blood counts (CBC) should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with persistent myelosuppression.

Bleeding Events: Dasatinib caused platelet dysfunction in vitro and thrombocytopenia in humans. Severe CNS...
hemorrhage, including fatalities, occurred in less than 1% of patients. Severe GI hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia. Caution is advised in patients required to take medications that inhibit platelet function or anticoagulants.

**Fluid Retention:** Fluid retention was severe in 8% of patients, including pleural and pericardial effusions reported in 5% and 1%, respectively. Severe ascites and generalized edema were each reported in 1%. Severe pulmonary edema was reported in less than 1% of patients. Patients who develop symptoms suggestive of pleural effusion (dyspnea or dry cough) should be evaluated by chest x-ray. Severe pleural effusion may require oxygen therapy and thoracentesis. Fluid retention was typically managed by supportive care measures that include diuretics or short courses of steroids. Patients over the age of 65 years are more likely to experience fluid retention events, and should be monitored closely.

**QT Prolongation:** \textit{In vitro} data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). Nine patients had QTc prolongation as an adverse event. Three patients (<1%) experienced a QTcF > 500 msec. SPRYCEL should be administered with caution in patients who have or may develop prolongation of QTc including patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome and patients taking anti-arrhythmic drugs, other medicinal products that lead to QT prolongation, or cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration.

**Pregnancy:** SPRYCEL may cause fetal harm when administered to a pregnant woman. Woman should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

**Drug Interactions:** Dasatinib is a CYP3A4 substrate. Drugs that may increase dasatinib concentrations are: Strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, ritonavir, atazanavir, indinavir, nefazodone, neflinavir, saquinavir, telithromycin and voriconazole). Comitant use of dasatinib and drugs that inhibit CYP3A4 should be avoided. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and dose reduction should be considered. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided. Drugs that may decrease dasatinib concentrations are: Strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital), which should be avoided. Alternative agents with less enzyme induction potential should be used or a dose increase of SPRYCEL should be considered. \textit{St. John's Wort} (\textit{Hypericum perforatum}) may decrease dasatinib plasma concentrations unpredictably. Patients taking SPRYCEL should not take \textit{St. John's Wort}.

Dasatinib is a time-dependent inhibitor of CYP3A4. Drugs that may have their plasma concentration altered by dasatinib are: CYP3A4 substrates with a narrow therapeutic index (eg, alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution.

Long-term suppression of gastric acid secretion by use of H2 blockers or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. Therefore, concomitant use of H2 blockers or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered. Simultaneous administration of SPRYCEL and antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL.

**Nursing Mothers:** It is unknown whether SPRYCEL is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue drug.

**Adverse Reactions:** The safety data reflect exposure to SPRYCEL in 2182 patients with leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Drug was discontinued for adverse reactions in 9% of patients in chronic phase, 10% in accelerated phase, 15% in myeloid blast phase CML, and 8% in lymphoid blast phase CML or Ph+ ALL.

The most frequently reported adverse reactions (reported in ≥20% of patients) included fluid retention events (37%), diarrhea (31%), headache (24%), skin rash (22%), nausea (22%), hemorrhage (21%), fatigue (21%), and dyspnea (20%). The most frequently reported serious adverse reactions included pleural effusion (9%), febrile neutropenia (4%), gastrointestinal bleeding (4%), pyrexia (3%), pneumonia (3%), dyspnea (3%), infection (2%), diarrhea (2%), congestive heart failure (2%), sepsis (1%), and pericardial effusion (1%).

Grade 3/4 laboratory abnormalities in clinical studies in chronic phase CML included neutropenia (46%), thrombocytopenia (41%), anemia (18%), hypophosphatemia (10%), and hypocalcemia (2%). Grade 3/4 elevations of transaminase or bilirubin and Grade 3/4 hypocalcemia and hypophosphatemia were reported in patients with all phases of CML, but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminase or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3/4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

**About Bristol-Myers Squibb**

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

\textit{This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995, regarding the research, development and commercialization of pharmaceutical products. 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 the clinical trials described in this release will support a regulatory filing. Forward-looking statements in the 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, 2008, its Quarterly Reports on Form 10-Q, and 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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