Four-Year Data from Phase 3 DASISION Trial Comparing Sprycel® (dasatinib) to Imatinib in First-Line Treatment of Adults with Ph+ CP-CML Presented at Annual Meeting of the American Society of Hematology

Release Date:
Monday, December 9, 2013 6:30 pm EST

Terms:
R&D News

Dateline City:
PRINCETON, N.J.

76% of Sprycel patients vs.63% of imatinib patients achieved a major molecular response

84% of Sprycel patients vs. 64% of imatinib patients achieved an optimal molecular response at three months (BCR-ABL ≤10%) as defined by treatment guidelines; patients who achieved this response had improved overall survival vs. those who did not

With four years of follow-up, the Sprycel safety profile was consistent with previously observed findings in this patient population

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) and Otsuka America Pharmaceutical, Inc. today announced four-year follow-up data from the Phase 3 DASISION study of Sprycel® (dasatinib) 100 mg once daily vs. imatinib (400 mg daily) in the first-line treatment of adults with Philadelphia chromosome-positive (Ph+) chronic phase chronic myeloid leukemia (CP-CML).

At four years, 76% of Sprycel patients vs. 63% of imatinib patients achieved a major molecular response (MMR). Additionally, 84% of Sprycel patients vs. 64% of imatinib patients achieved BCR-ABL ≤10% at three months, which is considered an optimal molecular response as defined by treatment guidelines (2013 European LeukemiaNet guidelines). Patients in both arms who achieved this response at three months had improved overall survival (OS) and progression-free survival (PFS) at four years vs. those who did not. At four years, 67% of Sprycel patients (n=172) and 65% of imatinib patients (n=168) remained on treatment. These data were presented today at the 55th Annual Meeting of the American Society of Hematology (Abstract #653).

Most drug-related adverse events occurred within the first year of treatment, and the types of safety events were consistent through year four. Adverse reactions reported in ≥10% of Sprycel-treated patients with newly diagnosed CP Ph+ CML were myelosuppression, fluid retention events (pleural effusion and superficial localized edema), diarrhea, headache, musculoskeletal pain, rash, and nausea. In Sprycel-treated patients, most grade 3-4 adverse events were hematologic lab abnormalities and occurred within the first year.

“These findings are based on four years of follow-up in patients and provide additional insights regarding the safety and efficacy of Sprycel in newly-diagnosed Ph+ CP-CML patients,” said Dr. Jorges E. Cortes, University of Texas M.D. Anderson Cancer Center. “These data also offer important insights on the potential impact that early responses might have on patient outcomes in this setting.”

“This longer term analysis from our Phase 3 trial provides further evidence of the sustained efficacy of Sprycel in the first-line setting and adds to our understanding of its safety in patients treated for several years,” said Michael Giordano, senior vice president, Head of Development, Oncology & Immunology, Bristol-Myers Squibb. “Sprycel remains an important therapy for many CML patients and we are committed to continuing its research in CML, with the goal of improving patient outcomes and informing medical practice.”

Initial data from SIMPLICITY, an ongoing observational cohort study of adult patients with newly diagnosed CP-CML receiving first-line treatment with Sprycel, imatinib or nilotinib in the U.S. or Europe will also be presented at the meeting. The study's
primary objective is to assess effectiveness of these tyrosine kinase inhibitors in clinical practice. The baseline data characterizing the study cohort were presented today in a poster session (Abstract #4026).

**DASISION Four Year Follow-Up Results**

In the DASISION study, at four years, 67% of Sprycel patients (n=172) and 65% of imatinib patients (n=168) remained on treatment. At four years, 76% of Sprycel patients vs. 63% of imatinib patients achieved MMR. Additionally, 53% of Sprycel patients achieved MR4 vs. 42% of imatinib patients, and 37% of Sprycel patients achieved MR4.5 vs. 30% of imatinib patients. In patients who achieved MMR, the median time to MMR for Sprycel and imatinib patients was 9.2 and 15.0 months, respectively. Through four years, transformation to accelerated or blast phase occurred in 12 patients receiving Sprycel and 18 patients receiving imatinib. PFS at four years was 90% in both arms and OS was 93% and 92% for Sprycel and imatinib, respectively.

In this study, based on an exploratory analysis, a proportion of patients in each arm achieved optimal molecular responses at six, nine, and 12 months, as defined by the 2013 European LeukemiaNet (ELN) guidelines. At 12 months, 84% of Sprycel patients vs. 64% of imatinib patients achieved an optimal molecular response (BCR-ABL ≤10%). In the Sprycel arm, PFS and OS rates at four years for patients who had BCR-ABL ≤10% at three months vs. those who did not were 92% vs. 67% (p=0.0004) and 95% vs. 83% (p=0.0092), respectively. In the imatinib arm, PFS and OS rates at four years for patients who had BCR-ABL ≤10% at three months vs. those who did not were 95% vs. 70% (p=0.0001) and 96% vs. 84% (p=0.0021), respectively.

At six months, 69% of Sprycel patients vs. 49% of imatinib patients achieved an optimal molecular response (BCR-ABL ≤1%) and at 12 months, 46% of Sprycel patients vs. 30% of imatinib patients achieved an optimal molecular response (BCR-ABL ≤0.1%).

Most drug-related adverse events occurred within the first year of treatment, and the types of safety events were consistent through year four. Adverse reactions reported in ≥10% of Sprycel-treated patients with newly diagnosed CP Ph+ CML were myelosuppression, fluid retention events (pleural effusion and superficial localized edema), diarrhea, headache, musculoskeletal pain, rash, and nausea. In Sprycel-treated patients, most grade 3-4 adverse events were hematologic lab abnormalities and occurred within the first year.

**About the DASISION Study**

DASISION (CA180-056) is an open-label, randomized, Phase 3 international trial of Sprycel 100 mg taken once-daily vs. imatinib 400 mg taken once-daily, in the treatment of newly-diagnosed CP Ph+ CML. The study enrolled 519 patients; 259 patients were randomized to receive Sprycel and 260 patients were randomized to receive imatinib. The primary study endpoint was confirmed complete cytogenetic response (CCyR) by 12 months. Select secondary endpoints were MMR at any time, time to MMR, and time to confirmed CCyR.

As published in the *New England Journal of Medicine* in 2010, in DASISION, 77% [95% CI, 71% - 82%] of patients treated with Sprycel (n=259) vs. 66% [95%, CI, 60% - 72%] of patients treated with imatinib (n=260) achieved the primary endpoint of confirmed CCyR (defined as two consecutive assessments of CCyR at least 28 days apart) by 12 months (p=0.007).

**About Sprycel® (dasatinib)**

Sprycel was first approved by the U.S. Food & Drug Administration (FDA) under accelerated review for the treatment of adults with CP Ph+ CML who are resistant or intolerant to prior therapy including imatinib in 2006. At that time, Sprycel was also approved for adults with Ph+ acute lymphoblastic leukemia (ALL) who are resistant or intolerant to prior therapy. Full approval was granted in May 2009. It is the first and only kinase inhibitor with survival data in its label for CP Ph+ CML patients who are resistant or intolerant to imatinib. Sprycel is now approved and marketed worldwide for these indications in more than 60 countries including the European Union (EU), Japan and Canada.

Sprycel is also an FDA-approved treatment for adults with newly diagnosed CP Ph+ CML (since October 2010). Sprycel received accelerated FDA approval for this indication. The effectiveness of Sprycel is based on cytogenetic response and major molecular response rates. The trial is ongoing and further data will be required to determine long-term outcome. Additional country approvals for this indication total more than 50.

**About Chronic Myeloid Leukemia**

CML is a type of leukemia in which the body produces an uncontrolled number of abnormal white blood cells. According to the most recent statistics, about 28,900 people are living with the disease in the United States. It is estimated that nearly 6,000 new cases will be diagnosed in 2013. CML occurs when pieces of two different chromosomes (chromosomes 9, 22) break off and attach to each other. There is no known cause for this genetic change to occur. The newly formed chromosome is called the Philadelphia chromosome, which contains an abnormal gene called *BCR-ABL* gene. This gene produces the BCR-ABL protein that is critical to the development of CML.

**SPRYCEL® (dasatinib) INDICATION & IMPORTANT SAFETY INFORMATION**

**INDICATION**

**SPRYCEL® (dasatinib) is indicated for the treatment of adults with:**

- Newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of SPRYCEL is based on cytogenetic and major molecular response rates. The trial is ongoing and further data will be required to determine long-term outcome

**IMPORTANT SAFETY INFORMATION**

**Myelosuppression:**
Treatment with SPRYCEL® (dasatinib) can cause severe (NCI CTC Grade 3/4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced phase 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 pre-existing laboratory abnormalities.

- Perform complete blood counts (CBCs) weekly for the first 2 months and then monthly thereafter, or as clinically indicated
- Myelosuppression was generally reversible and usually managed by dose interruption, dose reduction, or discontinuation
- Hematopoietic growth factor has been used in patients with resistant myelosuppression

Bleeding Related Events:

SPRYCEL caused platelet dysfunction in vitro and thrombocytopenia in humans. In all clinical trials, severe central nervous system (CNS) hemorrhage, including fatalities, occurred in 1% of patients receiving SPRYCEL. Severe gastrointestinal hemorrhage, including fatalities, 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. Exercise caution in patients required to take medications that inhibit platelet function or anticoagulants

Fluid Retention:

SPRYCEL is associated with fluid retention. In clinical trials, fluid retention was severe in up to 10% of patients. Severe ascites, pulmonary edema, and generalized edema were each reported in ≤1% of patients.
- Patients who develop symptoms suggestive of pleural effusion, such as dyspnea or dry cough, should be evaluated by chest X-ray
- Severe pleural effusion may require thoracentesis and oxygen therapy
- Fluid retention was typically managed by supportive care measures that included diuretics or short courses of steroids

QT Prolongation:

In vitro data suggest that SPRYCEL has the potential to prolong cardiac ventricular repolarization (QT interval).
- In 865 patients with leukemia treated with SPRYCEL in five phase 2 single-arm studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7.0 ms to 13.4 ms
- In clinical trials of patients treated with SPRYCEL (N=2440), 16 patients (1%) had QTc prolongation as an adverse reaction. Twenty-two patients (1%) experienced a QTcF >500 ms
- Administer SPRYCEL with caution to patients who have or may develop prolongation of QTc, including patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome and patients taking antiarrhythmic drugs, other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy
- Correct hypokalemia or hypomagnesemia prior to SPRYCEL administration

Congestive Heart Failure, Left Ventricular Dysfunction, and Myocardial Infarction:

Cardiac adverse reactions were reported in 7% of 258 patients taking SPRYCEL, including 1.6% of patients with cardiomyopathy, heart failure congestive, diastolic dysfunction, fatal myocardial infarction, and left ventricular dysfunction.
- Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately

Pulmonary Arterial Hypertension (PAH):

SPRYCEL may increase the risk of developing PAH, which may occur any time after initiation, including after more than one year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of SPRYCEL.
- Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL and during treatment. If PAH is confirmed, SPRYCEL should be permanently discontinued

Use in Pregnancy:

SPRYCEL may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of SPRYCEL in pregnant women.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant when taking 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 SPRYCEL

Drug Interactions:
SPRYCEL is a CYP3A4 substrate and a weak time-dependent inhibitor of CYP3A4.

- **Drugs that may increase SPRYCEL plasma concentrations are:**
  - **CYP3A4 inhibitors**: Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 should be avoided. If administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and a SPRYCEL dose reduction should be considered
  - **Strong CYP3A4 inhibitors** (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease or temporary discontinuation should be considered
    - **Grapefruit juice** may also increase plasma concentrations of SPRYCEL and should be avoided
  - **Drugs that may decrease SPRYCEL plasma concentrations are:**
    - **CYP3A4 inducers**: If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered
      - **Strong CYP3A4 inducers** (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) should be avoided. Alternative agents with less enzyme induction potential should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity
    - **St John's Wort** may decrease SPRYCEL plasma concentrations unpredictably and should be avoided
    - **Antacids** may decrease SPRYCEL drug levels. 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
    - **H2 antagonists/proton pump inhibitors** (eg, famotidine and omeprazole): Long-term suppression of gastric acid secretion by use of H2 antagonists or proton pump inhibitors is likely to reduce SPRYCEL exposure. Therefore, concomitant use of H2 antagonists or proton pump inhibitors with SPRYCEL is not recommended

- **Drugs that may have their plasma concentration altered by SPRYCEL are:**
  - **CYP3A4 substrates** (eg, simvastatin) with a narrow therapeutic index should be administered with caution in patients receiving SPRYCEL

**Adverse Reactions:**

The safety data reflect exposure to SPRYCEL in 258 patients with newly diagnosed chronic phase CML in a clinical trial (minimum of 36 months follow up; median duration of therapy was 37 months).

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Patients aged 65 years and older are more likely to experience toxicity. In the newly diagnosed chronic phase CML trial, the cumulative discontinuation rate was 9% with a minimum of 36 months follow up.

- In newly diagnosed chronic phase CML patients:
  - The most frequently reported serious adverse reactions included pleural effusion (4%), hemorrhage (2%), congestive heart failure (1%), pulmonary hypertension (1%), and pyrexia (1%)
  - The most frequently reported adverse reactions (reported in ≥10% of patients) included myelosuppression, fluid retention events (pleural effusion and superficial localized edema), diarrhea, headache, musculoskeletal pain, rash, and nausea
  - Grade 3/4 laboratory abnormalities included neutropenia (24%), thrombocytopenia (19%), anemia (12%), hypophosphatemia (7%), hypocalcemia (3%), elevated bilirubin (1%), and elevated creatinine (1%)
  - Grade 3/4 elevations of transaminase or bilirubin and Grade 3/4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML
  - 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

**Please see the full Prescribing Information at** [www.bms.com](http://www.bms.com).

**SPRYCEL is a registered trademark of Bristol-Myers Squibb Company.**

**About Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.**

Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd. are collaborative partners in the commercialization of Sprycel® (dasatinib) in the United States, Japan, and major European countries. Sprycel was discovered and developed by Bristol-Myers Squibb.

For more information about Bristol-Myers Squibb, visit [www.bms.com](http://www.bms.com) or follow us on Twitter at [http://twitter.com/bmsnews](http://twitter.com/bmsnews).

For information about Otsuka Pharmaceutical Co., Ltd., visit [www.otsuka-global.com](http://www.otsuka-global.com).

1 Major molecular response (MMR) is defined as a BCR-ABL transcript level of ≤0.1% (3 log reduction) as measured by real-time quantitative polymerase chain reaction (RQ-PCR) of peripheral blood.

2 Formal statistical comparison of MMR rates was only performed at the time of the primary endpoint (cCCyR within 12 months).

3 MR4 is defined as a 4-log reduction in BCR-ABL transcript from the standardized baseline (either detectable disease
≤0.01% BCR-ABL (IS) or undetectable disease in cDNA (in same volume used for BCR-ABL) with ≥10,000 ABL transcripts.

4 MR4.5 is defined as a 4.5-log reduction in BCR-ABL transcript from the standardized baseline (0.0032% IS, either detectable disease ≤0.0032% BRC-ABL (IS) or undetectable disease in cDNA (in same volume used for BCR-ABL) with ≥32,000 ABL transcripts.

5 Complete cytogenetic response (CCyR) is defined as the absence of Philadelphia chromosome-positive metaphases on cytogenetic assessment of bone marrow cells.