Observational Study Demonstrates No Greater Incidence of Progression to Acute Myeloid Leukemia with REVLIMID® in Patients with Lower-Risk Del(5q) Myelodysplastic Syndromes

BOUDRY, Switzerland, Dec 07, 2010 (BUSINESS WIRE) --

Celgene International Sàrl (NASDAQ: CELG) today announced the results of a comparative study evaluating the impact of REVLIMID® (lenalidomide) on the risk of progression to acute myeloid leukaemia (AML) in patients with low/int-1 risk myelodysplastic syndromes (MDS) with a del(5q) chromosome abnormality. These results were presented by investigators from the Groupe Francophone Des Myelodysplasies (GFM) during the 52nd Annual Meeting of the American Society of Hematology in Orlando, FL.

The study found no statistically significant difference in the risk of progression to AML from diagnosis of MDS between patients with red blood cell transfusion-dependent (RBC TD), lower risk MDS with del(5q) who were treated with lenalidomide and a comparable group of patients who were treated before lenalidomide was available. Likewise, no statistically significant survival difference was found between the two groups.

The study conducted by the GFM was initiated in response to concerns raised by the European Medicines Agency (EMA) that treatment with lenalidomide may trigger disease progression to AML in some MDS patients with del(5q). In this study, 95 RBC TD, lower risk MDS patients with del(5q), diagnosed between 1988 and 2007 in GFM centres, received 10 mg of lenalidomide/day in cycles of 3 weeks on, 1 week off. Rates of progression to AML and survival from MDS diagnosis of this group were compared to an historical control group of 99 similar patients with RBC TD lower risk MDS with del(5q) who were diagnosed between 1985 and 2005 and treated before lenalidomide was available.

In the analysis, 71 patients in each group were matched based on a propensity score, which compared characteristics such as gender, age at diagnosis, cytogenetics, and WHO and IPSS scoring. The 4-year cumulative incidence of AML from diagnosis was 8.9 percent in patients treated with lenalidomide and 15.8 percent in patients who did not receive lenalidomide (HR=0.46, 95% CI: 0.16-1.35; p=0.16). Median overall survival was 150 months in patients treated with lenalidomide versus 72.8 months in patients treated without lenalidomide (HR=0.54. 95% CI: 0.26-1.12; p=0.10).

About REVLIMID®

REVLIMID® is an IMiDs® compound. REVLIMID and other IMiDs continue to be evaluated in over 100 clinical trials. The IMiDs pipeline is covered by a comprehensive intellectual property estate of issued and pending patent applications in the US, EU and other regions, including composition-of- matter and use patents.

REVLIMID is approved in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy in nearly 50 countries, encompassing Europe, the Americas, the Middle-East and Asia, and in combination with dexamethasone for the treatment of patients whose disease has progressed after one therapy in Australia and New Zealand.

REVLIMID is also approved in the North America, South America, Asia and the Middle East for transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Marketing Authorization Applications are currently being evaluated in a number of other countries.

REVLIMID® (lenalidomide) in combination with dexamethasone is indicated for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy.

REVLIMID is indicated for patients with transfusion-dependent anaemia due to Low- or Intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Important Safety Information
WARNING: FETAL RISK, HEMATOLOGIC TOXICITY, and DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby. In women of childbearing potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Women of childbearing potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid fetal exposure to lenalidomide, REVLIMID is only available under a restricted distribution program called "RevAssist®."

Information about the RevAssist program is available at www.REVLIMID.com or by calling the manufacturer's toll-free number 1-888-423-5436.

HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors. (see DOSAGE and ADMINISTRATION)

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with MM who were treated with REVLIMID and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

CONTRAINDICATIONS:

Pregnancy Category X:

- Lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. Females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy

Allergic Reactions:

- REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

WARNINGS AND PRECAUTIONS:

Fetal Risk:

- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects. An embryofetal development study in non-human primates indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy. If REVLIMID is used during pregnancy, it may cause birth defects or death to a developing baby
- Females of childbearing potential must be advised to avoid pregnancy while on REVLIMID. Two effective contraceptive methods should be used during therapy, during therapy interruptions, and for at least 4 weeks after completing therapy
- Male Patients: It is not known whether lenalidomide is present in the semen of patients receiving the drug. Therefore, males receiving REVLIMID must always use a latex condom during any sexual contact with females of childbearing potential, even if they have undergone a successful vasectomy

Reproductive Risk and Special Prescribing Requirements (RevAssist Program):

- Because of this potential toxicity and to avoid fetal exposure, REVLIMID is only available under a special restricted distribution program called "RevAssist." Prescribers and pharmacists registered with the program can prescribe and
dispense the product to patients who are registered and meet all the conditions of the RevAssist program

Hematologic Toxicity--Multiple Myeloma:

- REVLIMID can cause significant neutropenia and thrombocytopenia
- Patients taking REVLIMID for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter
- In the pooled MM studies Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone
- Patients may require dose interruption and/or dose reduction

Deep Vein Thrombosis:

- Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with MM treated with lenalidomide combination therapy and patients with MDS treated with lenalidomide monotherapy

Allergic Reactions:

- Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions

Tumour Lysis Syndrome:

- Fatal instances of tumour lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken

Tumour Flare Reaction:

- Tumour flare reaction has occurred during investigational use of lenalidomide for chronic lymphocytic leukaemia (CLL) and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Treatment of CLL or lymphoma with lenalidomide outside of a well-monitored clinical trial is discouraged

DRUG INTERACTIONS:

- Erythropoietic agents, or other agents, that may increase the risk of thrombosis, such as oestrogen containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone

USE IN SPECIAL POPULATIONS:

Nursing Mothers:

- It is not known whether REVLIMID is excreted in human milk
- Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother

Geriatric Use:

- Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function

Renal Impairment:

- Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment (CLcr < 60 mL/min) and in patients on dialysis

ADVERSE REACTIONS:
Multiple Myeloma

- In the REVLIMID/dexamethasone treatment group, 269 patients (76%) underwent at least one dose interruption with or without a dose reduction of REVLIMID compared to 199 patients (57%) in the placebo/dexamethasone treatment group.
- Of these patients who had one dose interruption with or without a dose reduction, 50% in the REVLIMID/dexamethasone treatment group underwent at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group.
- Most adverse events and Grade 3/4 adverse events were more frequent in MM patients who received the combination of REVLIMID/dexamethasone compared to placebo/dexamethasone.
- Adverse reactions reported in greater-than or equal to 15% of MM patients (REVLIMID/dexamethasone vs. dexamethasone/placebo): fatigue (44% vs. 42%), neutropenia (42% vs. 6%), constipation (41% vs. 21%), diarrhea (39% vs. 27%), muscle cramp (33% vs. 21%), anaemia (31% vs. 24%), pyrexia (28% vs. 23%), peripheral oedema (26% vs. 21%), nausea (26% vs. 21%), back pain (26% vs. 19%), upper respiratory tract infection (25% vs. 16%), dyspnoea (24% vs. 17%), dizziness (23% vs. 17%), thrombocytopenia (22% vs. 11%), rash (21% vs. 9%), tremor (21% vs. 7%), weight decreased (20% vs. 15%), nasopharyngitis (18% vs. 9%), blurred vision (17% vs. 11%), anorexia (16% vs. 10%), and dyspepsia (15% vs. 10%).

Myelodysplastic Syndromes

- Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events observed in the del 5q MDS population.
- Other adverse events reported in greater-than or equal to 15% of del 5q MDS patients (REVLIMID): diarrhea (49%), pruritus (42%), rash (36%), fatigue (31%), constipation (24%), nausea (24%), nasopharyngitis (23%), arthralgia (22%), pyrexia (21%), back pain (21%), peripheral oedema (20%), cough (20%), dizziness (20%), headache (20%), muscle cramp (18%), dyspnoea (17%), pharyngitis (16%), epistaxis (15%), asthenia (15%), upper respiratory tract infection (15%).

DOSAGE AND ADMINISTRATION:

- Treatment is continued or modified based upon clinical and laboratory findings. Dosing modifications are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID.
- For other Grade 3 or 4 toxicities judged to be related to REVLIMID, hold treatment and restart at next lower dose level when toxicity has resolved to less-than or equal to Grade 2.

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS.

About Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a group of hematologic malignancies that affect approximately 300,000 people worldwide. Myelodysplastic syndromes occur when blood cells remain in an immature or "blast" stage within the bone marrow and never develop into mature cells capable of performing their necessary functions. Eventually, the bone marrow may be filled with blast cells suppressing normal cell development. MDS patients must often rely on blood transfusions to manage symptoms of anaemia and fatigue and may develop life-threatening iron overload and/or toxicity from frequent transfusions, thus underscoring the critical need for new therapies targeting the cause of the condition rather than simply managing its symptoms.

About Acute Myeloid Leukaemia

Acute Myeloid Leukaemia (AML) is a cancer of myeloid blood cells that often transforms from MDS upon disease progression. AML is the proliferation of abnormal cells that accumulate in the bone marrow and interfere with all types of normal blood cell production (multi-lineage dysplasia). AML has traditionally been treated with high intensity chemotherapy, which is poorly tolerated by the majority of the patients who are afflicted - the elderly. Many of these patients may go untreated and because they are ineligible for curative therapy, life expectancy is short and often measured in weeks to months.

About Deletion 5q Chromosomal Abnormality

Chromosomal (cytogenetic) abnormalities are detected in more than half of patients with myelodysplastic syndrome (MDS), and involve a deletion in all or part of one or more specific chromosomes. The most common cytogenetic abnormalities in MDS are deletions in the long arm of chromosomes 5, 7, and 20. Another common abnormality is an extra copy of chromosome 8. A deletion involving the 5q chromosome may be involved in 20 percent to 30 percent of all MDS patients. The World Health Organization has also recently identified a unique subset of MDS patients with a "5q- Syndrome" where the only chromosomal
abnormality is a specific portion of the 5q chromosome.

**About Celgene International Sàrl**

Celgene International Sàrl, located in Boudry, in the Canton of Neuchâtel, Switzerland, is a wholly owned subsidiary and international headquarters of Celgene Corporation. Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global pharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through gene and protein regulation. For more information, please visit the Company’s website at www.celgene.com.

*This release contains certain forward-looking statements which involve known and unknown risks, delays, uncertainties and other factors not under the Company’s control. The Company’s actual results, performance, or achievements could be materially different from those projected by these forward-looking statements. The factors that could cause actual results, performance, or achievements to differ from the forward-looking statements are discussed in the Company’s filings with the Securities and Exchange Commission, such as the Company’s Form 10-K, 10-Q and 8-K reports. Given these risks and uncertainties, you are cautioned not to place undue reliance on the forward-looking statements.*

SOURCE: Celgene International Sàrl

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