Study of REVLIMID® (lenalidomide) in Patients with High-Risk Asymptomatic Smoldering Multiple Myeloma Published in New England Journal of Medicine

Median time to progression to symptomatic disease and three-year overall survival measures were significantly improved in patients receiving REVLIMID and dexamethasone followed by REVLIMID maintenance compared with patients who did not receive treatment

BOUDRY, Switzerland--(BUSINESS WIRE)--Aug. 1, 2013-- Celgene International Sàrl, a wholly-owned subsidiary of Celgene Corporation (NASDAQ: CELG), today announced that data evaluating treatment with REVLIMID® (lenalidomide) in combination with dexamethasone followed by lenalidomide maintenance therapy in patients with high-risk asymptomatic smoldering multiple myeloma were published in the August 1 edition of The New England Journal of Medicine. Smoldering multiple myeloma is an early, asymptomatic form of the disease characterized by a 10% per year risk of progression to symptomatic disease over the first five years.

The Phase III, randomized, multicenter, open-label study, led by Maria-Victoria Mateos, M.D., Ph.D. from the Hospital Universitario de Salamanca on behalf of the Grupo Espanol de Mieloma (PETHEMA/GEM) evaluated whether treatment with the combination of lenalidomide and dexamethasone followed by lenalidomide maintenance in high-risk asymptomatic smoldering multiple myeloma patients prolonged time to progression to symptomatic disease compared with patients who did not receive active treatment and were just observed, which is the current standard of care for smoldering multiple myeloma.

The article detailed that after a median follow-up of 40 months, median time to progression to symptomatic disease, the primary endpoint of the study, was significantly longer in the treatment group compared with the observation group (not reached vs. 21 months; HR=0.18; p<0.001). The three-year overall survival rate from study inclusion was also higher in the treatment group compared with the observation group (94% vs. 80%; HR=0.31; p=0.03). A partial response was seen in 79% of the patients in the treatment group during induction, and 90% during the maintenance phase.

The most common Grade 3 adverse events in the treatment arm included infection (6%), asthenia (6%), neutropenia (5%) and rash (3%). No Grade 4 adverse events were reported. One patient had a Grade 5 adverse event, reported as a respiratory infection.

Second primary malignancies were reported in four patients in the treatment group (6%) and in one patient in the observation group (2%). Hematologic cancers were balanced between the arms with one patient in the treatment group having polycythemia vera (with a JAK2 mutation present in samples obtained at study entry), and one patient in the observation group having myelodysplastic syndromes. Breast cancer developed in one patient in the treatment group and prostate cancer developed in two patients in the treatment group (both of whom had a history of prostate hyperplasia with an elevated level of prostate-specific antigen).

Of 119 patients enrolled in Spain and Portugal, 57 were treated with lenalidomide (25 mg daily on days 1-21 of a 28-day cycle) and dexamethasone (20 mg on days 1-4 and 12-15 of a 28-day cycle) during a nine-cycle induction phase, and then continued treatment with a lower dose of lenalidomide (10 mg daily on days 1-21 of a 28-day cycle) during a maintenance phase. Total duration of therapy for the lenalidomide and dexamethasone arm (induction) plus REVLIMID maintenance could continue up to two years. The 62 patients in the observation group received no active treatment during the induction or maintenance phase, and were followed until disease progression. High-risk disease was defined as plasma-cell bone marrow infiltration of at least 10% and a monoclonal component (defined as an IgG level of ≥3 g per deciliter, an IgA level of ≥2 g per deciliter, or a urinary Bence Jones protein level of >1 g per 24 hours) or only one of the two criteria described above, plus at least 95% phenotypically aberrant plasma cells in the bone marrow plasma-cell compartment, with reductions in one or two uninvolved immunoglobulins of more than 25%, as compared with normal values.


These data are from an investigational study. REVLIMID® is not approved as a treatment for smoldering multiple myeloma.
About Smoldering Multiple Myeloma

Smoldering multiple myeloma is an early, slow-growing type of a cancer in which the plasma cells of the blood produce an excessive amount of abnormal, useless antibodies known as M proteins. People with the smoldering form of multiple myeloma are usually symptom-free and generally have normal blood counts, calcium levels and kidney function and lack bone and organ damage. As such, smoldering multiple myeloma is generally diagnosed based largely on laboratory findings, including M protein levels and the presence of abnormal plasma cells in the bone marrow.

On average, in the first five years following diagnosis, about 10 percent of patients with the smoldering form of the disease will progress to multiple myeloma each year. Thereafter, the percentage decreases to about five percent per year for the next five years.

About REVLIMID®

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 70 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 United States, Canada, Switzerland, Australia, New Zealand and several Latin American countries, as well as Malaysia and Israel, 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 and in Europe for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

In addition, REVLIMID is approved in the United States for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

U.S. Regulatory Information for Revlimid

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

REVLIMID® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

REVLIMID® (lenalidomide) is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

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 embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the “RevAssist®” program).

Information about the REVLIMID REMS™ Program is available at [www.cellgeneriskmanagement.com](http://www.cellgeneriskmanagement.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.

Venous Thromboembolism

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 thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient’s underlying risk factors.

CONTRAINDICATIONS

Pregnancy:

- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

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

Embryo-Fetal Toxicity:

- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys 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
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID

REVLIMID REMS™ Program

Because of embryo-fetal risk, REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) the REVLIMID REMS Program (formerly known as the “RevAssist®” Program). Prescribers and pharmacies must be certified with the program and patients must sign an agreement form and comply with the requirements. Further information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436

Hematologic Toxicity: REVLIMID can cause significant neutropenia and thrombocytopenia. MM: 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 trials 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. MCL: Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly
Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. Of these patients who had one dose interruption with or without a dose reduction, 76% (269/353) vs 57% (199/350), 50% (120/240) vs 28% (76/269), and 40% (96/240) vs 23% (58/252) 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. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Tumor Lysis Syndrome: Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Monitoring and evaluation for TLS is recommended in patients with MCL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to ? Grade 1. In the MCL trial, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion. Patients with Grade 1 or 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Second Primary Malignancies: Patients with MM treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

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, 76% (269/353) vs 57% (199/350), 50% (120/240) vs 28% (76/252), and 40% (96/240) vs 23% (58/252) 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.
- Grade 3/4 neutropenia occurred in 33.4% vs 3.4%; 2.3% experienced Grade 3/4 febrile neutropenia vs 0%.
- Deep vein thrombosis (DVT) was reported as a serious adverse drug reaction (7.4%) or Grade 3/4 (8.2%) compared to 3.1% and 3.4%. Discontinuations due to DVT were reported at comparable rates between groups.
- Pulmonary embolism (PE) was reported as a serious adverse drug reaction (3.7%) or Grade 3/4 (4.0%) compared to 0.9% and 0.9%. Discontinuations due to PE were reported at comparable rates between groups.
- Adverse reactions reported in ≥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%), anemia (31% vs 24%), pyrexia (28% vs 23%), peripheral edema (26% vs 21%), nausea (26% vs 21%), back pain (26% vs 19%), upper respiratory tract infection (25% vs 16%), dyspnea (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 dysgeusia (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
- Grade 3 and 4 adverse events reported in ≥ 5% of patients with del 5q MDS were neutropenia (53%), thrombocytopenia (50%), pneumonia (7%), rash (7%), anemia (6%), leukopenia (5%), fatigue (5%), dyspnea (5%), and back pain (5%)
- Other adverse events reported in ≥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 edema (20%), cough (20%), dizziness (20%), headache (20%), muscle cramp (18%), dyspnea (17%), pharyngitis (16%), epistaxis (15%), asthenia (15%), upper respiratory tract infection (15%)

Mantle Cell Lymphoma

- Grade 3 and 4 adverse events reported in ≥5% of patients treated with REVLIMID in the MCL trial (N=134) included neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), leukopenia (7%), fatigue (7%), diarrhea (6%), dyspnea (6%), and febrile neutropenia (6%)
- Serious adverse events reported in ≥2 patients treated with REVLIMID monotherapy for MCL included chronic obstructive pulmonary disease, clostridium difficile colitis, sepsis, basal cell carcinoma, and supraventricular tachycardia
- Adverse events reported in ≥15% of patients treated with REVLIMID in the MCL trial included neutropenia (49%), thrombocytopenia (36%), fatigue (34%), anemia (31%), diarrhea (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritus (17%), peripheral edema (16%), constipation (16%), and leukopenia (15%)
- Adverse events occurring in patients treated with REVLIMID in the MCL trial resulted in at least one dose interruption in 76 (57%) patients, at least one dose reduction in 51 (38%) patients, and discontinuation of treatment in 26 (19%) patients

DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in MM patients taking concomitant warfarin. Erythropoietic agents, or other agents, that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436

Nursing Mothers: It is not known whether REVLIMID is excreted in human milk. Because many drugs are excreted in human milk and 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

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established

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 (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis

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

About Celgene

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.

Forward-Looking Statements

This press release contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words “expects,” “anticipates,” “believes,” “intends,” “estimates,” “plans,” “will,” “outlook” and similar expressions. Forward-looking statements are based on management’s current plans, estimates, assumptions and projections, and speak only as of the date they are made. We undertake no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, many of which are discussed in more detail in our Annual Report on Form 10-K and our other reports filed with the Securities and Exchange Commission.

Source: Celgene International Sàrl

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