Celgene and LYSARC Provide Update on the Phase III ‘REMARC’ Study of REVLIMID® Maintenance Treatment in Patients with Diffuse Large B-Cell Lymphoma Responding to First-Line R-CHOP Therapy

SUMMIT, N.J. & LYON, France--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ: CELG) and the Lymphoma Study Association (LYSA) today announced that the Lymphoma Academic Research Organisation (LYSARC) reported initial data from a phase III, randomized, double-blind, international clinical study (REMARC). This investigational study evaluated maintenance therapy with REVLIMID® (lenalidomide) compared with placebo in diffuse large B-cell lymphoma (DLBCL) patients responding to first-line rituximab plus CHOP chemotherapy (R-CHOP) induction therapy. LYSARC sponsored the study under a Clinical Trial Agreement with Celgene.

REMARC achieved the primary endpoint of a statistically significant improvement in progression-free survival for patients receiving REVLIMID®. The interim analysis of overall survival, a key secondary endpoint, showed no benefit in the REVLIMID® arm. Based upon these interim results, Celgene does not currently plan to seek approval for this indication.

“We thank the patients and their families for participating in the REMARC trial and look forward to presenting these important data at a future hematology conference,” said Bertrand Coiffier, Professor of Hematology, Hospices de Lyon and University Claude Bernard Lyon 1 and Principal Investigator, REMARC.

“We are continuing to partner with LYSA to complete the analyses of the REMARC study,” said Michael Pehl, President Hematology and Oncology of Celgene. “We remain committed to finishing the four ongoing phase III trials evaluating REVLIMID® and are confident about its potential as a treatment option across different settings in lymphoma.”

A Broad Phase III Program in NHL Underway; Data from Additional Trials Expected in 2017

The REMARC study is part of a broad research program at Celgene focused on multiple areas of non-Hodgkin lymphoma. In addition to the REMARC study, REVLIMID® is also being evaluated in:

- RELEVANCE®, a combination with rituximab in previously untreated follicular lymphoma;
- AUGMENT®, a combination with rituximab in relapsed/refractory follicular and marginal zone lymphoma;
- MAGNIFY®, a combination with rituximab in relapsed/refractory follicular, marginal zone and mantle cell lymphoma; and,
- ROBUST®, a combination with R-CHOP in previously untreated ABC-subtype DLBCL.

Data from RELEVANCE® and AUGMENT® are expected in the first and second half of 2017, respectively. Beyond REVLIMID®, Celgene is also exploring multiple clinical candidates in non-Hodgkin lymphomas and T-cell lymphomas.

REVLIMID® is not approved for use in DLBCL.

About REMARC

REMARC is an international, multicentre, randomized, double-blind, placebo-controlled phase III study designed to explore the effect of maintenance therapy with REVLIMID® (lenalidomide) versus placebo on progression-free survival (PFS) in 650 patients treated with R-CHOP responding to induction therapy. Patients in REMARC had received at least 6 and up to 8 cycles of the R-CHOP 14 or R-CHOP 21 regimen or 6 R-CHOP-14 or -21 completed by 2 cycles of rituximab alone in accordance to local preferences. Evaluation of the response to R-CHOP was in accordance with Revised Response Criteria
for Malignant Lymphoma (2007). The primary endpoint of the study was progression-free survival. The secondary endpoints of the study included overall survival, event-free survival, response at the end of maintenance, improvement in response and safety.

**About REVLIMID®**

In the United States, REVLIMID® is approved in combination with dexamethasone for the treatment of patients with multiple myeloma. REVLIMID® is also 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 anemia due to low- or intermediate-1-risk myelodysplastic syndromes (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 MDS 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 (dex) is indicated for the treatment of patients with multiple myeloma (MM)

REVLIMID® 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® 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

REVLIMID® is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials

**Important Safety Information**

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL 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.celgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

**Hematologic Toxicity (Neutropenia and Thrombocytopenia)**
CONTRAINDICATIONS

Pregnancy: REVLIMID® can cause fetal harm when administered to a pregnant female and 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: See Boxed WARNINGS

- **Females of Reproductive Potential**: See Boxed WARNINGS
- **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: See Boxed WARNINGS: Prescribers and pharmacies must be certified with the REVLIMID® REMS® program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID®. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

Hematologic Toxicity: REVLIMID® can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. **MM**: Patients taking REVLIMID®/dex should have their complete blood counts (CBC) assessed every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter. **MDS**: 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 dose reduction. Please see the Black Box WARNINGS for further information. **MCL**: Patients taking REVLIMID® for MCL should have their CBCs monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction.

Venous and Arterial Thromboembolism: See Boxed WARNINGS: Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVLIMID®. Patients with known risk factors,
including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended and regimen is based on patients underlying risks. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision.

**Increased Mortality in Patients With CLL:** In a clinical trial in the first line treatment of patients with CLL, single agent REVLIMID® therapy increased the risk of death as compared to single agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in the REVLIMID® arm. REVLIMID® is not indicated and not recommended for use in CLL outside of controlled clinical trials.

**Second Primary Malignancies (SPM):** In clinical trials in patients with MM receiving REVLIMID®, an increase of invasive SPM notably AML and MDS have been observed. Monitor patients for the development of SPMs. Take into account both the potential benefit of REVLIMID® and risk of SPMs when considering treatment.

**Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID®/dex. 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.

**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. REVLIMID® capsules contain lactose; risk-benefit of treatment should be evaluated in patients with lactose intolerance.

**Tumor Lysis Syndrome (TLS):** Fatal instances of 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.

**Tumor Flare Reaction (TFR):** TFR has occurred during investigational use of lenalidomide for CLL and lymphoma. Monitoring and evaluation of TFR 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 REVLIMID® until TFR resolves to ≤ Grade 1. REVLIMID® may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion.

**Impaired Stem Cell Mobilization:** A decrease in the number of CD34+ cells collected after treatment ( > 4 cycles) with REVLIMID® has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

**ADVERSE REACTIONS**

**Multiple Myeloma**

- **In newly diagnosed:** The most frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm MPT (56%). There were more grade 3 and 4 and serious adverse reactions of infection in Arm Rd Continuous than either Arm MPT or RD18.

- The most common adverse reactions reported in ≥20% (Arm Rd Continuous): diarrhea (46%), anemia (44%), neutropenia (35%), fatigue (33%), back pain (32%), asthenia (28%), insomnia (28%), rash (26%), decreased appetite (23%), cough (23%), dyspnea (22%), pyrexia (21%), abdominal pain (21%), muscle spasms (20%), and thrombocytopenia (20%).

- **After at least one prior therapy** the most common adverse reactions reported in ≥20% (REVLIMID®/dex vs dex/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%), and weight
decreased (20% vs 15%)

**Myelodysplastic Syndromes**

- 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%)

- Adverse events reported in ≥15% of del 5q MDS patients (REVLIMID®): thrombocytopenia (61.5%), neutropenia (58.8%), 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%)

- 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%)

**DRUG INTERACTIONS**

Periodic monitoring of digoxin plasma levels is recommended due to increased Cmax and AUC with concomitant REVLIMID® therapy. Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dex and warfarin. Close monitoring of PT and INR is recommended in MM patients taking concomitant warfarin

**NURSING MOTHERS**

Discontinue drug or nursing taking into consideration the importance of the drug to the mother

**PEDIATRIC USE**

Safety and effectiveness in patients below the age of 18 have not been established

**RENAL IMPAIRMENT**

REVLIMID® is primarily excreted unchanged by the kidneys; adjustments to the starting dose are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis

Please see full Prescribing Information, including Boxed WARNINGS.

About Celgene

Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global biopharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through next-generation solutions in protein homeostasis, immuno-oncology, epigenetics, immunology and neuro-inflammation. For more information, please visit www.celgene.com. Follow Celgene on Social Media: @Celgene, Pinterest, LinkedIn, FaceBook and YouTube.

About LYSARC

The Lymphoma Academic Research Organisation (LYSARC), located in Lyon, France, is an academic clinical research organization running international clinical lymphoma trials in affiliation with the LYSA and in collaboration with other renowned, international cooperative groups. For more information, please visit www.lysarc.org.

About LYSA
The Lymphoma Study Association (LYSA), is a French association leader in international clinical and translational research in lymphoma, with a network of 130 centers in France, Switzerland, Portugal and Belgium. For more information, please visit www.lysa-lymphoma.org

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.


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