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Results of Phase III RELEVANCE Study Comparing REVLIMID plus Rituximab (R²) Versus Rituximab Plus Chemotherapy in Patients with Previously Untreated Follicular Lymphoma to be Presented at ASCO 2018

SUMMIT, N.J.--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG) today announced additional results from RELEVANCE, a phase III, randomized, open-label, international clinical study conducted in partnership with the Lymphoma Academic Research Organisation (LYSARC), were presented at the 54th Annual American Society of Clinical Oncology Scientific Sessions (ASCO) in Chicago, Illinois on June 1-5, 2018.

This investigational study evaluated REVLIMID[®] (lenalidomide) plus rituximab (R²), followed by R² maintenance, an investigational regimen, compared to the standard of care treatment of rituximab plus chemotherapy (R-chemo: R-CHOP, R-bendamustine or R-CVP) followed by rituximab maintenance in patients with previously untreated follicular lymphoma.

Investigators found that treatment with a chemotherapy-free R² regimen offered numerically similar efficacy results for the primary endpoints of progression free survival (PFS) and complete response or unconfirmed complete response (CR/CRu) at 120 weeks with a different safety profile than treatment with the conventional R-chemo standard. As previously disclosed, the study did not achieve the primary endpoints of superior PFS and CR/CRu.

"These findings provide important insight into the efficacy and safety of a chemotherapy-free regimen in patients with previously untreated follicular lymphoma and represent an important step forward in understanding possible treatment options for these patients," said Nathan Fowler, MD, Associate Professor, Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center.

The co-primary efficacy endpoints of the study were CR and CRu at 120 weeks and PFS during the pre-planned analysis (final analysis of CR/CRu and interim analysis of PFS). An analysis of the findings found that 48% of patients in the R² arm and 53% of those receiving R-chemo maintained CR/CRu 120 weeks after randomization, with a 3-year estimated interim PFS rate of 77% and 78% respectively (P=0.48, HR (95% CI) 1.10 (0.85-1.43)). Preliminary overall survival, one of the study's secondary endpoints, showed a 3-year survival rate of 94% in both treatment arms. Other secondary endpoints included number of patients with adverse events, time to treatment failure, event-free survival, time to next anti-lymphoma treatment, time to next chemotherapy treatment, overall response rate at 120 weeks based on International Working Group (IWG) 1999 criteria, and health-related quality of life as measured by the EORTC QLQ-C30.

The majority of patients in both arms completed treatment (69% R² and 71% R-chemo). The most common Grade 3/4 TEAEs in both arms were neutropenia (32% R² vs. 50% R-chemo), febrile neutropenia (2% R² vs. 7% R-chemo) and cutaneous events (7% R² vs. 1% R-chemo). SPMs were reported in 7% R² and 10% R-chemo patients, and Grade 5 AEs were 1% in both treatment arms.

"We believe the findings of the RELEVANCE trial add further to the understanding of the R² regimen in patients with follicular lymphoma," said Nadim Ahmed, President of Hematology and Oncology for Celgene. "We now look forward to the results of our AUGMENT study, which is evaluating this important regimen in previously treated patients with indolent lymphomas. These studies support our ongoing efforts to develop a portfolio of novel treatments for lymphoma."

REVLIMID alone or in combination with rituximab is not approved for use in follicular lymphoma in any country.

ABOUT RELEVANCE

RELEVANCE is the first multi-center, international, open-label, randomized phase III clinical trial of the chemotherapy-free combination immunotherapy R² vs. R-chemo followed by rituximab maintenance in previously untreated, advanced follicular lymphoma patients. The study was conducted by Celgene in the US and Japan and by LYSARC in the rest of the world at 136 centers in 10 countries and evaluated the safety and efficacy of REVLIMID plus rituximab (R²) followed by R²

maintenance compared to the standard of care treatment of rituximab plus chemotherapy (R-CHOP, R-bendamustine or R-CVP) followed by rituximab maintenance.

The trial evaluated 1030 patients with advanced follicular lymphoma who had not received prior treatment and were deemed to require treatment per Groupe d'Etude des Lymphomes Folliculaires (GELF) Criteria. Patients received treatment for 120 weeks and were randomized to receive either R² or R-chemo treatment. The median age of the patients was 59 years.

The R² arm received REVLIMID + Rituximab on the following dosing schedules: REVLIMID 20-mg on days 2-22 every 28 days for up to 6 cycles. Patients with a complete response after 6 cycles then received REVLIMID 10-mg on days 2-22 every 28 days for 12 cycles. Patients with a partial response after 6 cycles continued to receive REVLIMID 20 mg for 3-6 cycles until they achieved a CR/CRu, at which time they then received REVLIMID 10 mg on days 2-22 of every 28-day cycle for up to 9 or 6 cycles, respectively. Patients who remained in partial response after the additional 6 cycles received REVLIMID 10 mg for a total of 18 cycles. Rituximab 375 mg/m² was administered on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; 8 weeks later responding patients continue with 375 mg/m² rituximab every 8 weeks for 12 cycles.

The R-chemo arm received ONE of the following: Rituximab - CHOP (72%), Rituximab - CVP (5%), or Rituximab - Bendamustine (23%). Seven to 8 weeks later, responding patients continued with 375 mg/m² rituximab every 8 weeks for 12 cycles.

About REVLIMID[®]

REVLIMID[®] (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of patients with multiple myeloma (MM)

REVLIMID is indicated as maintenance therapy in patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT)

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.

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)

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 and Arterial Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

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 risk to the fetus

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

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: See Boxed WARNINGS

- 1 **Females of Reproductive Potential: See Boxed WARNINGS**
- 1 **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 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- 1 **Blood Donation:** Patients must not donate blood during treatment with REVLIMID and for 4 weeks 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 or REVLIMID as maintenance therapy 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 the regimen should be based on patient's 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 hematologic plus solid tumor SPM, notably AML and MDS, have been observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment

Increased Mortality with Pembrolizumab: In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials

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

Severe Cutaneous Reactions Including Hypersensitivity Reactions: Angioedema and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash, or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. 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, TEN, or DRESS is suspected and should not be resumed following discontinuation for these reactions

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 for 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

Thyroid Disorders: Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before start of REVLIMID treatment and during therapy

Early Mortality in Patients with MCL: In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline ($\geq 10 \times 10^9/L$)

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 $\geq 20\%$ (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%)
- | **Maintenance Therapy Post Auto-HSCT:** The most frequently reported Grade 3 or 4 reactions in $\geq 20\%$ (REVLIMID

arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm

- | The most frequently reported adverse reactions in $\geq 20\%$ (REVLIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 32%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (5%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (55%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 21%)
- | **After at least one prior therapy:** The most common adverse reactions reported in $\geq 20\%$ (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 $\geq 5\%$ 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 $\geq 15\%$ 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 $\geq 5\%$ 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 $\geq 15\%$ 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 C_{max} 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 patients with MM taking concomitant warfarin

USE IN SPECIFIC POPULATIONS

- | **PREGNANCY: See Boxed WARNINGS:** If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436
- | **LACTATION:** There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID
- | **PEDIATRIC USE:** Safety and effectiveness have not been established in pediatric patients
- | **RENAL IMPAIRMENT:** Adjust the starting dose of REVLIMID based on the creatinine clearance value 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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Celgene Corporation

Investors:

+1-908-673-9628

ir@celgene.com

or

Media:

+1-908-673-2275

media@celgene.com

Source: Celgene Corporation

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