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Data Presented on REVLIMID® (lenalidomide) Compared with Investigators' Choice in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Exploratory analysis in heavily pre-treated patients, in response and survival measures were reported in hard-to-treat patients

Phase III ROBUST study will evaluate REVLIMID plus R-CHOP in hard-to-treat patients

SAN FRANCISCO--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG) today announced that results were presented from a phase II/III study (DLC-001) of REVLIMID® (lenalidomide) compared with investigators' choice (IC) of therapy in patients with relapsed/refractory diffuse large b-cell lymphoma (DLBCL) were presented during the 56th American Society of Hematology annual meeting.

In this study, presented by Myron Czuczman, M.D., the data suggest improved response rates, progression-free survival and overall survival with lenalidomide compared with IC in the non-germinal b-cell (GCB) population as defined by immunohistochemistry (IHC). These improved outcomes appeared more pronounced in the activated b-cell (ABC) sub-type when assessed by gene expression profiling.

Patients with both GCB and ABC DLBCL sub-types treated with lenalidomide had a similar overall response rate, but significant progression-free survival (PFS) and overall survival (OS) compared to IC.

Patients with GCB DLBCL treated with lenalidomide had an ORR of 26.1% (n=23/102; p=.279) compared to 28.6% in non-GCB DLBCL patients treated with lenalidomide (n=28/102; p=.179) per IHC. The data suggested greater improvements in PFS and OS with lenalidomide (15.1 weeks PFS; p=.021; HR 0.50 [CI 95%, 0.27-0.92]; 32.3 weeks OS; p=.253; HR 0.70 [CI 95%, 0.38-1.30]) compared to IC (7.1 weeks PFS; p=.021; HR .50 [CI 95%, 0.27-0.92]; 20.4 weeks OS; p=.253; HR 0.70 [CI 95%, 0.38-1.30]) in the non-GCB patients. Patients in the ABC subtype as defined by GEP had improved ORR of 45.5% (n=11/102; p=.206) compared to 18.8% in those treated with IC (n=16/102; p=.206). There were also significantly improved PFS rates in the ABC subtype of patients treated with lenalidomide versus IC (82.0 weeks PFS vs. 6.2 weeks PFS, respectively; p=.105; HR 0.44 [CI 95%, 0.15-1.23]) as well as OS rates (108.4 weeks vs. 18.6 weeks; p=.144; HR 0.47 [CI 95%, 0.17-1.33]).

All patients, regardless of subtype or therapy group, experienced one or more treatment-emergent adverse event, with neutropenia, anemia, and thrombocytopenia being the most common.

"Patients with ABC-type DLBCL have been historically difficult to treat," said Dr. Czuczman. "The results of this study demonstrate that lenalidomide may play an important role in optimizing the treatment of individual subtypes of diffuse large B-cell lymphoma."

Based on the results of this study, Celgene will open the ROBUST study evaluating lenalidomide plus rituximab, cyclophosphamide, doxorubicin, prednisone and vincristine (R^2CHOP) compared with placebo plus R-CHOP in patients who have untreated ABC-type DLBCL. The study will utilize GEP subtyping through Celgene's collaboration with NanoString Technologies.

REVLIMID is not indicated for the treatment of DLBCL in any country.

About DLC-001

This randomized, multicenter, open-label, phase II/III study was conducted to determine the efficacy and safety of single-agent lenalidomide vs. single-agent investigator's choice (IC) in relapsed/refractory DLBCL patients who received at least two prior therapies, or were ineligible for stem cell transplantation or further combination chemotherapy. DLBCL subtype (GCB vs non-GCB) was determined by a central pathology lab using immunohistochemistry (IHC) per the Hans method (Hans 2004). Patients were stratified by subtype, then randomized 1:1 to receive lenalidomide (25 mg/day, 21 days of 28-day cycle) or IC (gemcitabine, rituximab, etoposide, or oxaliplatin) until progressive disease (PD), unacceptable toxicity, or voluntary withdrawal. In the event of radiologically confirmed PD, patients in the IC arm were allowed to cross over to lenalidomide. The primary endpoint for Stage 1 was overall response rate (ORR), as determined by an Independent Response Assessment Committee.

Progression-free survival (PFS), overall survival (OS) and subtype analysis using gene expression profiling (GEP) were exploratory endpoints. Concordance of GEP and IHC was evaluated from three separate laboratories. Prespecified criterion to advance to Stage 2 was a two-sided 15 percent significance level in ORR in favor of lenalidomide based on IHC-defined subtype. The data did not fulfill this requirement, and stage 2 was not opened.

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

REVLIMID is not indicated and 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)

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 dex 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. 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.celgenerisk management.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 dex 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 thereafter. In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients. Patients may require dose interruption and/or dose reduction. See **Boxed WARNINGS**

Venous and Arterial Thromboembolism: A significantly increased risk of DVT (7.4%) and PE (3.7%) occurred in patients

with MM treated with REVLIMID and dex compared to the placebo and dex group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with MM who were treated with REVLIMID and dex therapy compared with placebo and dex (0.6%, and 0.9%) in clinical trials. 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). In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events occurred in patients with refractory and relapsed MM who were treated with REVLIMID and dex compared to 8.3% thrombosis in the placebo and dex group. Median time to first thrombosis event was 2.7 months. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision. **See Boxed WARNINGS**

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. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08-3.41] consistent with a 92% increase in risk of death. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials

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

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dex. 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

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 REVLIMID treatment should be evaluated in patients with lactose intolerance

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

Tumor Flare Reaction: Tumor flare reaction (TFR) has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials

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 lenalidomide until TFR resolves to ≤ Grade 1. In the MCL trial, approximately 10% of subjects experienced TFR; all reports were Grade 1 and 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

ADVERSE REACTIONS

Multiple Myeloma

- In the REVLIMID/dex 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/dex treatment group
- Of these patients who had one dose interruption with or without a dose reduction, 76% (269/353) vs 57% (199/350), 50% in the REVLIMID/dex treatment group underwent at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dex treatment group
- Most adverse events and Grade 3/4 adverse events were more frequent in MM patients who received the combination of

REVLIMID/dex compared to placebo/dex

- 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/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%), 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 dex 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 after making a benefit-risk assessment in patients receiving REVLIMID

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.

About Celgene

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 www.celgene.com. Follow us on Twitter @Celgene as well.

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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