LENALIDOMIDE, REVLIMID®

CC-5013-MCL-003

A PHASE 3 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIRST-LINE MAINTENANCE STUDY OF LENALIDOMIDE (REVLIMID®) IN PATIENTS WITH MANTLE CELL LYMPHOMA

(The "RENEW" Trial)

Indication studied:	*First-line maintenance treatment in mantle cell lymphoma subjects who are ineligible for autologous or allogeneic transplant and have achieved complete or partial response after first-line combination chemotherapy*
Developmental phase of study:	*Phase 3*
First subject enrolled:	*15 Apr 2010*
Last subject completed:	*02 Mar 2011*
Release date of report:	*16 Jun 2011*

Company/Sponsor signatory: *Celgene Corporation*

9900 W. 109th Street
Overland Park, KS 66210 U.S.A.
TN
FAX

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Sponsor's Responsible Medical Officer: _____ _____
Date

SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Revlimid® Capsules		
Name of Active Ingredient: Lenalidomide		

Title of study: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled, First-line Maintenance Study of Lenalidomide (Revlimid®) in Patients with Mantle Cell Lymphoma

Coordinating principal investigator:

Investigators: Seven investigators in the Czech Republic, France, Italy, Portugal, Russia, and the United States randomized subjects.

Study centers: Nine study centers screened subjects and 7 study centers (2 in France and 1 each in Czech Republic, Italy, Portugal, Russia, and the United States) randomized subjects.

Publications (reference): None

Studied period (years): **Date first subject enrolled:** 15 Apr 2010 **Date last subject completed:** 02 Mar 2011	**Phase of development:** 3

Objectives:

Primary: To evaluate the efficacy of lenalidomide as maintenance therapy after completion of first-line combination chemotherapy in patients with mantle cell lymphoma (MCL) who are not candidates for transplantation and have achieved partial response (PR) or complete response (CR).

Secondary: To evaluate the safety of lenalidomide as maintenance therapy after completion of first-line combination chemotherapy in patients with MCL who are not candidates for transplantation and have achieved partial or complete response.

Exploratory: To investigate tumor response by minimal residual disease (MRD) status assessment; To investigate the association of the biological profile in diagnostic tumor tissue, on patient response to lenalidomide maintenance therapy.

Methodology:

This phase 3, multicenter, double-blind, randomized, placebo-controlled study of oral lenalidomide monotherapy as first-line maintenance treatment in MCL subjects was conducted in 3 phases: screening/baseline, treatment, and follow-up phases.

Screening/baseline phase: Subjects who had undergone a first-line induction chemotherapy regimen were eligible for screening once they had received the last planned dose of the first-line induction chemotherapy and achieved a PR or CR. Screening procedures were completed within 12 weeks after the last dose of the first-line chemotherapy and included collection of baseline disease characteristics, eg, tumor/lymph node biopsy; prior lymphoma therapy; MCL International Prognostic Index (MIPI) score (optional); lymphoma-related symptoms; Eastern Cooperative Oncology Group (ECOG) performance status; physical examinations; radiology assessments (CT scan or MRI) of neck, chest, abdomen, and pelvis; target and non-target lesion measurements.

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Treatment phase: Eligible subjects were randomized in a 1:1 ratio to one of two treatment arms:

- Lenalidomide once daily on Days 1 to 21 of every 28-day cycle
- Placebo once daily on Days 1 to 21 of every 28-day cycle

Randomization was stratified according to 1) the type of first-line induction chemotherapy (anthracycline-based, fludarabine-based, or rituximab-bendamustine combination therapy) and 2) the response to first-line induction chemotherapy (CR or PR).

The treatment phase for each subject started with first intake of study drug (Cycle 1, Day 1) and continued for a maximum of 2 years or until disease progression, development of unacceptable toxicity, or voluntary withdrawal.

Efficacy assessments scheduled to be performed during the treatment phase included physical examinations; radiology assessments; and target and non-target lesion measurements; and response assessments. Safety assessments during the treatment phase included collecting information on incidence of adverse events, hospitalizations, and prior/concomitant medications; hematology and serum chemistry laboratory evaluations; assessments of lymphoma-related symptoms and ECOG performance status; vital sign measurements; and 12-lead electrocardiograms.

Exploratory assessments included evaluations of minimal residual disease (MRD) status, molecular and acquired genetic alterations as well as any changes in gene expression involved in lymphomagenesis, and health-related quality of life.

Follow-up phase: Subjects who completed 2 years in the treatment phase or discontinuation treatment for any reason (except for withdrawal of consent) were to be followed every 90 days (±14 days). The study was to continue until 80% of the patients had died or 5 years from the last patient randomized, whichever came first.

Number of subjects (planned and analyzed):

Planned: Approximately 382 (191 in each arm) subjects

Analyzed: 9 subjects

Diagnosis and main criteria for inclusion: Histologically-proven MCL (including evidence of cyclin D1 overexpression by immunohistochemistry), transplant ineligibility, and completion of first-line induction chemotherapy where response of a PR or CR was achieved.

Test product, dose and mode of administration, batch number: Oral lenalidomide 15 mg was administered once daily on Days 1 to 21 of every 28-day cycle. Subjects with moderate renal insufficiency (creatinine clearance ≥ 30 mL/min but < 60 mL/min) received a lower dose of 5 mg once daily on Days 1 to 21 of every 28-day cycle. In addition to the 15-mg capsules, Celgene also supplied 5-mg and 10-mg lenalidomide capsules for dose reductions. The lot numbers of the packaged lenalidomide were 09F0441.2 for the 15-mg capsules; 09F0441.1 for the 10-mg capsules; 09F0440.1 for the 5-mg capsules, QD dosing; and 09F0439.1 for the 5-mg capsules, QOD dosing.

Duration of treatment: Subjects were to receive study drug for a maximum of 2 years or until disease progression, development of unacceptable toxicity, or voluntary withdrawal, whichever came first. This study was prematurely terminated and subjects who remained active eventually discontinued

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treatment due to study closure by the Sponsor.

Reference therapy, dose and mode of administration, batch number: Placebo capsules were identical in appearance to the lenalidomide capsules and contained the inactive ingredients of the lenalidomide formulation. Placebo 15 mg was administered once daily on Days 1 to 21 of every 28-day cycle. Subjects with moderate renal insufficiency (creatinine clearance ≥ 30 mL/min but < 60 mL/min) received a lower dose of 5 mg once daily on Days 1 to 21 of every 28-day cycle. In addition to the 15-mg capsules, Celgene also supplied 5-mg and 10-mg placebo capsules for dose reductions. The lot numbers of the packaged placebo were 09F0441.3 for the 15-mg and the 10-mg capsules; 09F0440.2 for the 5-mg capsules, QD dosing; and 09F0439.2 for the 5-mg capsules, QOD dosing.

Criteria for evaluation:

Efficacy: Not applicable.

Safety: Incidence of adverse events, clinical laboratory evaluations (hematology, serum chemistry), and vital signs measurements.

Statistical methods:

Analysis of efficacy was not performed for this prematurely terminated study. Analysis of safety included data from all subjects who received at least one dose of study drug (safety population). Subject exposure to study drug was summarized by treatment arm including the duration of treatment exposure, average daily dose, and number of cycles. Safety was assessed by evaluating the incidence of adverse events, clinical laboratory data, and vital signs. Adverse events were tabulated by system organ class and preferred term, which were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 10.0. Adverse events and their severity were classified using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Treatment-emergent adverse events suspected by the investigator to be related to the study drug and serious treatment-emergent adverse events were summarized by treatment arm. Clinical laboratory data and vital signs information were presented as subject data listings.

SUMMARY – CONCLUSIONS

This study was prematurely terminated by the sponsor in light of new unpublished data that rendered the current design of the study no longer clinically relevant. A study design with the control arm of no active treatment was no longer appropriate. The termination of the trial was not based on any safety concerns in the study.

STUDY SUBJECTS:

Nine subjects were enrolled in the study. All subjects received at least one dose of study drug and were included in the safety population. Four subjects were randomized to the lenalidomide arm and 5 subjects were randomized to the placebo arm. One subject in the lenalidomide arm discontinued treatment due to an adverse event and one subject in the placebo arm discontinued treatment due to disease progression; the remainder of the subjects discontinued treatment due to study closure or sponsor decision.

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The median age of the subjects was 76.0 years (range: 65.0 to 84.0 years). Six of the 9 subjects were males, and all were White/Caucasian. Three of 4 subjects in the lenalidomide arm and 1 of 5 subjects in the placebo arm had a response of CR to the first-line induction chemotherapy prior to entering the study. The remainder achieved a response of PR to the first-line induction chemotherapy prior to entering the study.

EFFICACY RESULTS:

Not applicable.

SAFETY RESULTS:

The median duration of exposure to the study drug was 91.0 days (range: 49.0 to 245.0 days) in the lenalidomide arm and 133.0 days (range: 45.0 to 162.0 days) in the placebo arm. The median average daily dose was similar in both arms, 15.0 mg.

All 4 subjects in the lenalidomide arm and 4 of 5 subjects in the placebo arm experienced at least 1 adverse event. None of the adverse events were reported by more than 1 subject in either treatment arm. Three subjects in the lenalidomide arm and 2 subjects in the placebo arm had adverse events that were suspected by the investigator to be related to the study drug. One subject in each treatment arm had at least one grade 3/4 adverse event.

There were no incidences of tumor flare or tumor lysis in the study. None of the subjects experienced any venous thromboembolic events.

No subject died during the conduct of the study. One lenalidomide-treated subject, who had a history of basal cell carcinoma, had a serious adverse event of squamous cell carcinoma (spinocellular carcinoma on right palpebral, grade 3) that was suspected by the investigator to be related to the study drug. This was the only serious adverse event reported in the study and also the only adverse event that caused discontinuation of the study drug. This subject also experienced malignant melanoma (melanoma on cheek, grade 3), basal cell carcinoma (basocellular carcinoma cervical right, grade 2; and infiltrant carcinoma baso-cellular frontal lesion, grade 3), and squamous cell carcinoma (infiltrant spinocellular carcinoma frontal lesion, grade 3) during the study. All these malignancies were suspected by the investigator to be related to the study drug.

Neutropenia (grade 3) experienced by one subject in the lenalidomide arm and thrombocytopenia (grade 3) experienced by one subject in the placebo arm were the only adverse events that led to dose interruptions or reductions.

Abnormalities were noted in the hematology and serum chemistry parameters but none of these led to treatment discontinuation. Results of vital signs measurements did not show issues of clinical concern.

CONCLUSION:

Overall, based on the known safety profile of lenalidomide, no new safety concerns were identified in this prematurely terminated phase 3 study of lenalidomide as a first-line maintenance treatment in patients with mantle cell lymphoma.

Date of the report:

16 Jun 2011