2. 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 (CC-5013)		

Title of Study: A Phase 2, Multicenter, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of Single-Agent Lenalidomide (Revlimid®) in Subjects with Relapsed or Refractory T-Cell Non-Hodgkin's Lymphoma; The "Expect" Trial

Principal Investigator:

Investigators: A total of 39 investigators enrolled subjects.

Study center(s): A total of 26 study centers (2 in the United States, 16 in France, 2 in Belgium, and 6 in Australia) enrolled subjects.

Publications (reference): None

Studied period (years): Date first patient enrolled: 16 Jun 2008 Date last patient completed: 6 Apr 2010	Phase of development: 2

Objectives:

Primary:

- To determine the efficacy of lenalidomide monotherapy in relapsed or refractory T-cell non-Hodgkin's lymphoma (NHL). Efficacy will be assessed by measuring the response rate, tumor control rate, duration of response, time to progression and progression free survival.

Secondary:

- To evaluate the safety of lenalidomide monotherapy as treatment for subjects with relapsed or refractory T-cell NHL.

Methodology:

CC-5013-TCL-001 was a phase 2, multicenter, single-arm, open-label study of oral lenalidomide monotherapy administered to subjects with relapsed or refractory T-cell lymphoma. This study was conducted in two phases: a Treatment Phase and a Follow-up Phase.

Potential study subjects were screened for protocol eligibility within 28 days prior to the start of lenalidomide therapy. In addition, the following assessments were performed: evaluation to rule out central nervous system (CNS) lymphoma, blood pressure, pulse, weight, height, 12-lead electrocardiogram (ECG), hematology and chemistry labs, thyroid function tests (free T3, free T4, and serum thyroid stimulating hormones [TSH]), pregnancy test for females of childbearing potential

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Revlimid® Capsules	Volume:	
Name of Active Ingredient: Lenalidomide (CC-5013)	Page:	

(FCBPs), physical examination (including lymphadenopathy, hepatomegaly, and splenomegaly), ECOG performance status, CT or MRI, target and non-target lesion measurements, and bone marrow aspirate and biopsy.

Treatment Phase:

Subjects who qualified for enrollment into the study entered the Treatment Phase and received single-agent lenalidomide 25 mg once daily (QD) on Days 1-21 every 28 days (28-day cycles). Subjects with moderate renal insufficiency (creatinine clearance ≥ 30 mL/min but ≤ 60 mL/min) received a starting dose of 10 mg. The Treatment Phase for each subject began on Study Day 1. Study visits were scheduled to occur every 28 days to coincide with the beginning of a new cycle. However, if the start date of a new cycle was delayed due to the development of an adverse event (AE), the visit date was to be scheduled once the patient had taken a total of 21 days of study drug followed by a 7-day rest period (equivalent to a 28-day cycle period). Serial assessments of safety and efficacy were to be performed as outlined in the Schedule of Study Assessments or as directed in the dose modification guidelines (Appendix 16.1.1).

The following assessments were to be performed on Day 1 (± 7 days) of each cycle: adverse event query, concomitant medication query, blood pressure, pulse, weight, hematology and chemistry labs, pregnancy testing for FCBPs, physical examination (including lymphadenopathy, hepatomegaly, and splenomegaly), ECOG performance status and lenalidomide counseling. Thyroid function tests (free T3, free T4, and serum thyroid stimulating hormone [TSH]) were to be performed on Day 1 (± 7 days) of each odd cycle. Every 56 days after Day 1 (± 7 days), a CT or MRI, target or non-target lesion measurements, a response assessment, a progression-free survival assessment, and a bone marrow aspirate and biopsy (only in subjects whose baseline aspirate/biopsy was positive for lymphoma and only if the subject had otherwise fulfilled the criteria for complete response [CR]) were to be performed.

Subjects were evaluated for AEs at each visit with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 used as a guide for the grading of severity. The dose of lenalidomide for each subject was interrupted and modified following toxicity as described in Appendix 16.1.1.

It was suggested that subjects receive tumor lysis prophylaxis (allopurinol or equivalent) and be well hydrated during the first 7 days of lenalidomide treatment in the first cycle or as clinically indicated. It was also suggested that any tumor flare occurring during the first 1-2 weeks of Cycle 1 be recorded as an AE and not as progressive disease (PD) and be treated symptomatically first with non-steroidal anti-inflammatory agents (NSAIDs) or narcotics and in severe cases with prednisone until symptom resolution. To monitor for tumor lysis syndrome and cytopenia(s), the subjects were to have a complete blood count (CBC) and chemistry drawn on Days 2 and 4 of the first cycle and additionally as clinically indicated.

Subjects considered to be at high risk for developing deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial thrombosis were to receive prophylactic aspirin, low molecular weight heparin, or warfarin unless contraindicated. High risk was defined as having a history of DVT or PE, a significant family history of DVT or PE, a performance status of ≥ 2, a history of smoking, use of oral contraceptives, or concurrent use of epoetin. Subjects with diabetes mellitus or coronary artery disease were considered to be at high risk for arterial thromboembolic events.

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 (CC-5013)		

Subjects could continue participation in the Treatment Phase of the study for a maximum duration of 24 months, or until disease progression or unacceptable AEs developed.

Follow-up Phase:

All subjects who discontinued the Treatment Phase for any reason continued to be followed until progression of disease or until next lymphoma treatment was given, whichever came first, during the Follow-up Phase.

This study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and all applicable regulatory requirements including those set forth in the Code of Federal Regulations (CFR) Title 21 Parts 50 and 56 and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. An internal Celgene data monitoring committee (DMC) was to review ongoing safety data throughout the study. In addition, an independent radiology review committee (IRC) was to perform a blinded, independent assessment of response (including the development of progressive disease [PD]). However, since the study was terminated prematurely, no DMC reviews occurred and a blinded, independent assessment of response via an IRC was no longer required.

Number of patients (planned and analyzed):

Eighty subjects planned, 54 enrolled and analyzed

Diagnosis and main criteria for inclusion:

Subjects with biopsy-proven peripheral T-cell NHL (PTCL; any subtype) or cutaneous T-cell NHL (CTCL; only the subtype mycosis fungoides) who had relapsed or were refractory to previous therapy for T-cell NHL. Subjects must have had measureable disease on cross-sectional imaging (CT or MRI) at least 2 cm in the longest diameter. Subjects must have received at least one prior combination chemotherapy regimen containing at least two cytotoxic agents. In addition, subjects must have had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

Test product, dose and mode of administration, batch number: Celgene supplied 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules of lenalidomide. The finished lot numbers were: 09F0327 for the 2.5-mg capsules, 07F0182, 08F0316, and 09F0328 for the 5-mg capsules, 07F0183, 08F0317, and 09F0329 for the 10-mg capsules, 09F0330 for the 15-mg capsules, 07F0184, 08F0318, and 09F0331 for the 20-mg capsules, and 07F0185 and 08F0258 for the 25-mg capsules.

Duration of treatment:

Subjects were to receive study drug for 24 months or until disease progression or unacceptable AEs developed.

Reference therapy, dose and mode of administration, batch number:

Not applicable

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 (CC-5013)		

Criteria for evaluation:

Efficacy:

The efficacy assessments performed were response rate (as measured by cross-sectional imaging) and date of documentation of disease progression. Baseline and on-study response assessments must have been performed using an identical technique. Tests which may have been done included CT or MRI scanning of measurable and non-measurable lesions and bone marrow biopsy. Response and progression were evaluated using the international criteria proposed by the 1999 International Workshop Lymphoma Response Criteria (IWLRC) for target lesions.

Safety:

The safety assessments performed included physical examination, electrocardiogram (ECG), blood pressure and pulse, hematology and chemistry laboratory tests, serum thyroid function tests, serum/urine beta-human chorionic gonadotropin (β-hCG; FCBPs only), AEs, and concomitant medications.

Statistical methods:

Data from the safety population (all enrolled subjects who received at least one dose of study drug) were included in the safety analyses. Adverse events and their severity were classified using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) when possible. Adverse event frequency was tabulated by system organ class (SOC) and MedDRA version 13.0 preferred term (PT). In the by-subject analysis, a subject having the same event more than once was counted only once. Adverse events were summarized by worst NCI CTCAE grade. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, study-drug-related events, and serious AEs were listed separately. Laboratory data was graded according to NCI CTCAE severity grade.

SUMMARY – CONCLUSIONS

This study was terminated prematurely because a preliminary assessment of the study data revealed a low response rate. There had been no safety issues to warrant closure of this study.

EFFICACY RESULTS:

Not applicable for this abbreviated clinical study report.

STUDY PATIENTS:

A total of 54 subjects were enrolled in the study; all of whom received at least 1 dose of the study drug and were included in both the Intent-to-Treat (ITT) and the Safety populations. All subjects discontinued the study and 8 subjects whom the investigator felt would benefit from continued treatment were able to continue therapy with commercial REVLIMID. The reasons for study drug discontinuation were: disease progression (37.0%), adverse event (29.6%), other (22.2%), death, lack of therapeutic effect, and subject withdrew consent (3.7% each). The term “other” includes 8 subjects who discontinued the study at study termination, 3 subjects who underwent a bone marrow transplant, and 1 subject who experienced disease progression. The reasons for study discontinuation were: disease progression (50.0%), other (18.5%), adverse event (11.1%), death (9.3%), subject started new lymphoma treatment (7.4%), and subject withdrew consent (3.7%). The term “other” includes 9 subjects who

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Revlimid® Capsules	Volume:	
Name of Active Ingredient: Lenalidomide (CC-5013)	Page:	

discontinued the study at study termination and 1 subject who discontinued to undergo an allogenic transplant. Subject had moderate renal insufficiency and received a starting dose of 10 mg QD. All other subjects had a starting dose of 25 mg QD.

SAFETY RESULTS:

The duration of drug exposure ranged from 3 days to 252 days.

The percentage of subjects who reported at least 1 AE was 98.1% (53 subjects), with 74.1% (40 subjects) reporting an AE considered by the investigator to be related to study drug. At least 1 serious adverse event (SAE) was reported in 29 (53.7%) subjects; 16 (29.6%) of these subjects reported an SAE considered to be related to lenalidomide. At least 1 AE leading to study drug discontinuation was reported in 21 (38.9%) of subjects, and at least 1 AE leading to dose interruption/reduction was reported in 19 (35.2%) of subjects.

Common AEs reported by ≥ 10% of subjects were:

- Blood and Lymphatic System Disorders: thrombocytopenia (24.1%; 13 subjects), neutropenia (16.7%; 9 subjects), and anemia (14.8%; 8 subjects)
- Gastrointestinal Disorders: constipation (22.2%; 12 subjects), diarrhea (14.8%; 8 subjects), nausea (13.0%; 7 subjects), dysphagia (11.1%; 6 subjects), and vomiting (11.1%; 6 subjects)
- General Disorders and Administration Site Conditions: pyrexia (29.6%; 16 subjects), asthenia (22.2%; 12 subjects), and edema peripheral (14.8%; 8 subjects)
- Investigations: weight decreased (11.1%; 6 subjects)
- Nervous System Disorders: headache (11.1%; 6 subjects)
- Respiratory, Thoracic, and Mediastinal Disorders: dyspnoea (14.8%; 8 subjects)
- Skin and Subcutaneous Tissue Disorders: rash (11.1%; 6 subjects)

Common AEs related to study drug reported by ≥ 10.0% of subjects were:

- Blood and Lymphatic System Disorders: thrombocytopenia (11.1%; 6 subjects)
- Gastrointestinal Disorders: constipation (13.0%; 7 subjects)
- General Disorders and Administration Site Conditions: asthenia (11.1%; 6 subjects) and pyrexia (11.1%; 6 subjects)

This AE profile is consistent with the known adverse event profile for single-agent lenalidomide.

SAEs were reported in 29 (53.7%) subjects. Serious adverse events reported in ≥ 2 subjects were: dyspnoea (4 subjects; 7.4%), neutropenia, thrombocytopenia, general physical health deterioration, and pneumonia (reported in 3 subjects each; 5.6%), and anemia, febrile neutropenia, asthenia, pyrexia, sepsis, decreased appetite, and syncope (reported in 2 subjects each; 3.7%). A total of 16 (29.6%) subjects experienced an SAE considered by the investigator to be related to lenalidomide. Study drug-

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Revlimid® Capsules	Volume:	
Name of Active Ingredient: Lenalidomide (CC-5013)	Page:	

related SAEs reported in ≥ 2 subjects included febrile neutropenia, neutropenia, and thrombocytopenia (reported in 2 subjects each; 3.7%).

Grade 3/4 AEs were reported in 34 (63.0%) subjects. Of the grade 3/4 AEs reported in at least 2 subjects, thrombocytopenia was reported in 11 subjects (20.4%), neutropenia was reported in 8 subjects (14.8%), dyspnoea was reported in 4 subjects (7.4%), rash was reported in 3 subjects (5.6%), and abdominal pain, anemia, asthenia, dysphagia, febrile neutropenia, general physical health deterioration, leukopenia, nausea, edema peripheral, pain, pneumonia, sepsis, and tumor flare were reported in 2 subjects each (3.7%). Grade 3/4 AEs considered by the investigator to be related to study drug were reported in 19 (35.2%) subjects. The grade 3/4 study drug-related AEs reported in ≥ 2 subjects were: thrombocytopenia (5 subjects; 9.3%), neutropenia (4 subjects; 7.4%), and febrile neutropenia, leukopenia, rash, and tumor flare (reported in 2 subjects each; 3.7%).

Grade 5 AEs were reported in 8 (14.8%) subjects. Acute respiratory distress syndrome, cerebral ischemia, dyspnoea, lung infiltration, metastasis, neutropenic sepsis, peripheral T-cell lymphoma unspecified, and pneumonia were reported in one subject (1.9%) each. Of these, only the event of neutropenic sepsis was considered by the investigator to be related to study drug. A total of 12 (22.2%) subjects died within 30 days of last dose of study drug. Half of these deaths (11.1%) were due to disease progression. The other causes of death listed (in one subject [1.9%] each) were acute respiratory distress, complications of neutropenic sepsis, dyspnoea, general status alteration, hemolytic anemia, and respiratory insufficiency due to new infection (pulmonary).

Shifts from non-clinically significant values at baseline to NCI CTCAE grade 3/4 values were noted in chemistry and hematology parameters. Although four subjects experienced an AE within the Investigations System Organ Class (SOC) (blood albumin decreased, blood lactate dehydrogenase increased, blood magnesium decreased, blood phosphorus increased, and blood potassium decreased were reported in one subject each), there were no discontinuations due to shifts in chemistry parameters. Approximately 20% of subjects exhibited a shift to NCI CTCAE grade 3/4 values in platelet count, absolute neutrophil count, and white blood cell count. However, few subjects (≤ 3.7%) discontinued the study due to thrombocytopenia, neutropenia or febrile neutropenia.

The adverse events of interest, identified based upon the known mechanism-of-action or class effects of lenalidomide, summarized in this study were venous thromboembolic events, tumor flare/tumor lysis syndrome, and neutropenic sepsis. No venous thrombolic AEs occurred during this study. Four (7.4%) subjects experienced an AE of tumor flare, three of whom had an event considered by the investigator to be related to study drug. There were a total of 7 tumor flare events: five events were considered by the investigator to be related to study drug, two events were grade 3, three events were grade 2, and two events were grade 1 in severity, and 1 event was serious and led to study drug discontinuation. One subject experienced both tumor flare (grade 2) and tumor lysis syndrome (grade 3). Neither of these events was serious, considered to be related to lenalidomide treatment, or resulted in dose interruption/reduction or discontinuation of study drug. One (1.9%) subject had a grade 5 AE of neutropenic sepsis 12 days after starting lenalidomide treatment and died due to complications from neutropenic sepsis.

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 (CC-5013)		
CONCLUSION: Overall, based upon the known safety profile of lenalidomide, no new safety concerns were identified in this prematurely terminated phase 2 study of lenalidomide monotherapy for the treatment of relapsed or refractory T-cell non-Hodgkin's lymphoma (NHL). Date of the report: February 3, 2011		