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		

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 Aggressive Non-Hodgkin's Lymphoma

Coordinating Principal Investigator:

Investigators: A list of investigators and their institutional affiliations are provided in Appendix 16.1.4.

Study center(s): 58 study centers were initiated into the protocol and 48 centers in 7 countries (US, Canada, United Kingdom, Spain, Germany, France, and Italy) enrolled subjects.

Publications (reference):

Czuczman MS, Vose J, Zinzani P, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma: Results from an international study (NHL-003). J Clin Oncol 27, 2009 (suppl; abstr e19504).

Reeder CB, Witzig TE, Zinzani PL, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle-cell lymphoma: Results from an international study (NHL-003). J Clin Oncol 27:7s, 2009 (suppl; abstr 8569).

Reeder CB, Vose J, Witzig TE, et al. Lenalidomide (LEN) in patients with transformed lymphoma: Results from a large international phase II study (NHL-003). J Clin Oncol 28:7s, 2010 (suppl; abstr 8037).

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22(7):1622-1627.

Studied period (years):	**Phase of development:**
Date first patient enrolled: 26 Oct 2006 **Date last patient completed:** 27 Apr 2011	2

Objectives:

Primary: To determine the efficacy of lenalidomide in relapsed or refractory aggressive non-Hodgkin lymphoma (NHL). Efficacy was assessed by measuring the overall response rate (ORR), complete response rate, duration of response, duration of complete response, progression-free survival (PFS), time to progression (TTP), time to first response, and overall survival (OS).

Secondary: To evaluate the safety of lenalidomide monotherapy as treatment for subjects with relapsed or refractory aggressive NHL.

Methodology:

This phase 2, multicenter, single-arm, open-label study of oral lenalidomide monotherapy in subjects with relapsed or refractory aggressive NHL was conducted in 2 phases: a treatment phase and a follow-up phase.

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Treatment Phase. Subjects who qualified for enrollment into the study entered the treatment phase and received single-agent lenalidomide 25 mg once daily on Days 1 to 21 of every 28-day cycle. The treatment phase began on Day 1 of Cycle 1. Study visits were scheduled to occur every 28 days to coincide with the beginning of a new cycle. The start date of a new cycle was delayed if adverse events occurred, in which case the visit date for the start of the following cycle was scheduled 28 days after the actual start date of the delayed cycle. Efficacy and safety assessments, including complete blood count (CBC) evaluations occurred at least every 2 weeks during Cycles 1 to 4 during the treatment phase. Subjects could remain in the treatment phase until disease progression or unacceptable adverse events developed.

Follow-up Phase

During the follow-up phase, all subjects who discontinued treatment for any reason were followed until study closure for disease progression, start of next anti-lymphoma treatment, and death.

Number of subjects:

Planned: 200 subjects
Enrolled; 218 subjects
Analyzed: 217 subjects

Diagnosis and main criteria for inclusion: Diagnosis of aggressive NHL, measurable disease on cross-sectional imaging of at least 2 cm in the longest diameter, at least one prior treatment regimen for lymphoma, and relapsed or refractory to previous therapy.

Test product, dose and mode of administration, batch number:

Lenalidomide was supplied in bottles containing twenty-one 25 mg capsules. Bottles containing twenty-one capsules of 10 mg lenalidomide or 5 mg lenalidomide were also provided for dosage reductions.

The 25 mg lenalidomide supply came from the following batch/lot numbers: 06F0094, 06F0193, 07F0212, 08F0058, and 10F0078.
The 10 mg lenalidomide supply came from the following batch/lot numbers: 06F0093, 06F0162, 08F0057, and 10F0077.
The 5 mg lenalidomide supply came from the following batch/lot numbers: 06F0092, 06F0161, 07F0211, 08F0056, and 10F0076

Duration of treatment:

Subjects continued participation in the treatment phase of the study until disease progression developed or lenalidomide treatment was discontinued for any reason.

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

Not applicable

Criteria for evaluation:

Efficacy: Primary. ORR (CR + Complete response unconfirmed [CRu] + Partial response [PR]). Secondary. Complete response rate (CR + CRu); duration of response; duration of complete response; PFS; TTP; time to first response; and OS. Exploratory analyses were also conducted to investigate correlation between response and prognostic variables.

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

Statistical methods:

The primary end point was the ORR, defined as the proportion of subjects assessable for response whose best response was CR, CRu, or PR. Secondary efficacy measures were complete response rate, defined as the proportion of subjects assessable for response whose best response was CR, or CRu; duration of response; duration of complete response; PFS; TTP; time to first response, and OS. Response to treatment and disease progression, along with the corresponding dates, were assessed by a blinded, centralized independent review committee (Central Review) according to the International Workshop Lymphoma Response Criteria (IWLRC) (Cheson, 1999). Duration of response was calculated as the time from the first response assessment demonstrating evidence of at least a PR to the first documentation of disease progression or death due to NHL, whichever occurred first. Duration of complete response was calculated as the time from the first response assessment demonstrating evidence of at least a CRu to the first documentation of disease progression or death due to NHL, whichever occurred first. Progression-free survival was defined as the time from the start of study drug therapy to the first observation of disease progression or death due any cause, whichever occurred first. Time to progression was defined as the time from the start of study drug therapy to the first documentation of progressive disease. Time to first response was defined as the time from the start of study drug therapy to the time to at least a PR. Overall survival was defined was defined as the days between the first dosing day to the death day (due to any cause). The Kaplan-Meier method was used to estimate the duration of response, duration of complete response, TTP, PFS, and OS.

The possible correlation of ORRs and specific demographic and disease-related baseline characteristics were investigated using the 2-sided Fisher's exact test. Data from all subjects treated with at least one dose of lenalidomide were included in the safety analysis. Adverse events and their severity were classified using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) Version 3.0.

Evaluation of subgroups was performed for all efficacy and safety parameters. Subgroups included subjects diagnosed with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), grade 3 follicular lymphoma (FLgr3), and transformed lymphoma (TSF).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Overall response rate (ORR). The primary efficacy endpoint was the ORR based on the Central Review. A total of 68 subjects of 217 in the ITT population had a best response of at least a PR for an ORR of 31.3%. The 68 subjects included 7 subjects with CR, 21 with CRu, and 40 with PR (see Summary of Efficacy Analysis table below).

The ORR for subjects with MCL (N = 57) was 35.1%, which included 20 who responded (2 CR + 5 CRu + 13 PR). The ORR for subjects with DLBCL (N = 108) was 24.1%, which included 26 who responded (2 CR + 8 CRu + 16 PR). The ORR for subjects with FLgr3 (N = 19) was 42.1%, which included 8 who responded (1 CR + 2 CRu + 5 PR). The ORR for subjects with transformed lymphoma

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(N = 33) was 42.4%, which included 14 who responded (2 CR + 6 CRu + 6 PR).

Complete response rate. The overall complete response rate was 12.9%. The complete response rates in subjects with, MCL, DLBCL, FLgr3 and TSF were 12.3%, 9.3%, 15.8% and 24.2%, respectively.

Summary of Efficacy Analysis (ITT Population)

Efficacy Variable	All Subjects (N = 217)	NHL Subtype			
		MCL Subjects (N = 57)	DLBCL Subjects (N = 108)	FLgr3 Subjects (N = 19)	TSF Subjects (N = 33)
ORR (%) [a], (95% CI)[b]	**31.3** (25.23, 37.96)	**35.1** (22.91, 48.87)	**24.1** (16.37, 33.25)	**42.1** (20.25, 66.50)	**42.4** (25.48, 60.78)
Complete response rate (%)[c], (95% CI)[b]	**12.9** (8.75, 18.11)	**12.3** (5.08, 23.68)	**9.3** (4.53, 16.37)	**15.8** (3.38, 39.58)	**24.2** (11.09, 42.26)
DoR, Median (months) [d], (95% CI)	**18.4** (6.51, 34.06)	**16.3** (7.10, NE)	**4.1** (2.14, 18.4)	**21.0** (4.27, NE)	**26.9** (18.71, NE)
DoC, Median (months) [d], (95% CI)	**28.3** (19.20, NE)	**NE** (9.70, NE)	**NE** (5.33, NE)	**23.7** (19.20, 28.27)	**21.4** (9.53, NE)
PFS time, Median (months) [d], (95% CI)	**4.5** (3.68, 6.28)	**8.8** (5.49, 22.98)	**3.6** (1.94, 3.91)	**7.5** (5.59, 36.03)	**4.3** (1.87, 25.02)
TTP time, Median (months) [d], (95% CI)	**4.5** (3.68, 6.28)	**8.8** (5.49, 22.98)	**3.6** (1.94, 3.91)	**7.5** (5.59, 36.03)	**4.3** (1.87, 28.77)
Time to first response, Median (months) [e], (Min, Max)	**1.9** (1.4, 43.4)	**1.9** (1.6, 24.2)	**1.9** (1.7, 43.4)	**1.9** (1.4, 2.1)	**2.0** (1.7, 3.9)
OS time, Median (months) [f], (95% CI)	**25.8** (20.09, NE)	**NE** (NE, NE)	**12.5** (7.40, NE)	**NE** (16.21, NE)	**25.0** (18.54, NE)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DLBCL = diffuse large B-cell lymphoma; DoC = duration of complete response; DoR = duration of response; FLgr3 = follicular lymphoma, grade 3; ITT = intent-to-treat; MCL = mantle cell lymphoma; Max = maximum; Min = minimum; NE = not estimable; NHL = non-Hodgkin lymphoma; ORR = overall response rate; OS = overall survival; PR = partial response; PFS = progression-free survival; TSF = transformed lymphoma; TTP = time to progression.

[a] Overall response rate = CR + CRu + PR.

[b] CI is an exact confidence interval from the binomial distribution.

[c] Complete response rate = CR + CRu.

[d] The median was based on the Kaplan-Meier estimate.

[e] Time to first response = time to first CR or CRu or PR.

[f] Overall survival was based on Investigator data.

Note: Response was defined as the best treatment result during the trial without starting any non-study anti-lymphoma treatment.

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Duration of Response. The overall median duration of response to treatment was 18.4 months. The longest median duration of response was noted in subjects with TSF (26.9 months). The median durations of response in subjects with FLgr3, MCL, and DLBCL were 21.0, 16.3, and 4.1 months, respectively.

Duration of Complete Response. The overall median duration of complete response to lenalidomide treatment was 28.3 months. The median duration of response was not reached for subjects with MCL or DLBCL, and was 23.7 and 21.4 months for subjects with FLgr3 and TSF, respectively.

Progression-free Survival. The overall median PFS was 4.5 months. The longest median PFS time noted was in the MCL subgroup (8.8 months). The median PFS time for FLgr3, TSF, and DLBCL subjects was 7.5 months, 4.3 months, and 3.6 months, respectively.

Time to Progression. Time to progression was identical to PFS. The overall median TTP was 4.5 months. The longest median TTP time noted was in the MCL subgroup (8.8 months). The median TTP time for FLgr3, TSF, and DLBCL subjects was 7.5 months, 4.3 months, and 3.6 months, respectively

Time to First Response. The overall median time to first response (CR, CRu, or PR) was 1.9 months (range: 1.4 to 43.4 months), which was similar in all of the subgroups.

Overall survival: The overall median OS time 25.8 months. The median OS had not been reached in MCL and FLgr3 subjects, and was 12.5 months for DLBCL subjects and 25.0 months for TSF subjects.

SAFETY RESULTS:

The safety of lenalidomide monotherapy administered at a dose of 25 mg once daily for the first 21 days of repeated 28-day cycles to subjects who were relapsed or refractory to previous therapy for lymphoma was consistent with the known safety profile for lenalidomide. The median duration of exposure to the study drug was 63.0 days (range: 2 to 1050 days). The adverse events were predominantly hematologic, and were successfully treated in most cases.

The most common adverse events were neutropenia (47.5%) and thrombocytopenia (32.7%). Other frequently reported adverse events included fatigue (29.0%), anemia (27.6%), constipation (27.2%), diarrhea (24.0%), pyrexia (22.6%), and nausea (21.2%). Neutropenia (43.3%), thrombocytopenia (28.6%), fatigue (20.7%), and anemia (20.3%) were the most common study drug-related adverse events. The most common grade 3/4 adverse events were neutropenia (41.5%), thrombocytopenia (20.7%), and anemia (9.2%). The median duration of grade 4 neutropenia and grade 4 thrombocytopenia were 8 days and 12 days, respectively.

Fifteen subjects had VTEs or other thromboembolic events. There were 7 subjects with tumor flare during treatment Cycle 1 that all resolved within 30 days. One subject had a grade 3 tumor flare that started 3 days after the first dose of study drug that was considered a serious adverse event. Study drug was interrupted and restarted at a lower dose once the tumor flare resolved with treatment after 8 days. One subject had 2 events of TLS assessed by the investigator, but neither event met any of the criteria of TLS upon further examination of the data (no observation of hyperkalemia, hyperuricemia, hyperphosphatemia, or hypocalcemia in serum chemistry evaluations, and no observation of arrhythmia, seizure, or sufficient impairment of creatinine clearance).

Of the 217 subjects who received lenalidomide, 12 were diagnosed with second primary malignancies (SPMs). Nine subjects were diagnosed during the treatment phase of the study. Four of these 9 subjects had invasive SPMs (AML, prostate cancer, renal cell cancer, and gastric cancer). The duration of

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lenalidomide treatment and time-to-onset of the 4 invasive SPMs from the first dose of lenalidomide ranged from 48 days / 38 days (Subject ; prostate cancer) to 454 days / 455 days (Subject ; renal cell cancer). All 4 subjects had received prior cytotoxic chemotherapy agents (4 subjects had been treated with alkylating agents and 3 subjects had also received topoisomerase II inhibitors) and all 4 subjects had previous exposure to rituximab. Three of the 4 subjects have died due to the SPM. The remaining 5 subjects with SPMs that were diagnosed during the treatment phase of the study had noninvasive, non-melanoma skin cancer (NMSC) SPMs. These 5 subjects had been heavily pretreated with cytotoxic chemotherapy and all 5 subjects remained alive at the date of last contact.

An additional 3 subjects were diagnosed with SPMs after study discontinuation and are not in the clinical database. Two of these subjects had invasive SPMs (MDS and esophageal carcinoma) and 1 subject had 3 separate NMSCs. One subject (MDS) received only 14 days of lenalidomide treatment and the SPMs of MDS and esophageal carcinoma occurred 3 to 4 years after the start of lenalidomide. These subjects also had received previous treatments with alkylating agents, topoisomerase II inhibitors, and rituximab. One subject committed suicide and the other 2 subjects (MDS and NMSCs) were alive at the last date of contact.

Thirty-one subjects died 30 days or less from the last dose of study drug and 61 subjects died altogether (including during post-treatment follow-up). The majority of deaths (70.5%; 43/61 subjects) were due to progressive disease. Serious adverse events occurred in 47.0% of subjects and SAEs that were assessed by the investigator as study-drug related occurred in 19.8% of subjects.

Adverse events leading to discontinuation of the study drug were reported in 27.2% of the subjects and the frequencies of individual events reported were low. Adverse events causing dose reductions or interruptions reported in 56.7% of the subjects. Neutropenia (31.8%) and thrombocytopenia (17.1%) were the primary reasons for dose reductions or interruptions.

The distribution of treatment-emergent adverse events was generally similar between the MCL and DLBCL subtypes. There was a higher frequency of study drug-related treatment-emergent adverse events in MCL Subjects (89.5%) compared to DLBCL Subjects (75.9%), consistent with a longer median exposure to study drug for subjects with MCL (100 days versus 46 days, respectively).

Other than the expected hematological effects, lenalidomide therapy had no notable effects on the clinical laboratory results.

CONCLUSION:

The results from this phase 2 study demonstrate the activity and favorable benefit-risk profile of oral lenalidomide monotherapy in subjects with relapsed or refractory aggressive NHL and warrant further investigation of lenalidomide therapy, alone or in combination, in the treatment of subjects with aggressive NHL.

Date of the report:

23 Jul 2012