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 1 Multi-Center, Open-Label Study of the Safety and Efficacy of a Stepwise Dose-Escalation Schedule of Lenalidomide Monotherapy in Subjects with Relapsed or Refractory B-Cell Chronic Lymphocytic leukemia (B-Cell CLL)

Principal investigators:

Study center(s):

Publications (reference):

None

Studied period (years): Date first patient enrolled: 25 Jan 2007 Date last patient completed: 25 Feb 2010	Phase of development: 1

Objectives:

Primary:

To evaluate the safety of lenalidomide when administered by a stepwise dose-escalation schedule in subjects with relapsed or refractory B-cell CLL

Secondary:

To evaluate the efficacy of a stepwise dose–escalation schedule of lenalidomide in subjects with relapsed or refractory B–cell CLL

Methodology:

CC-5013-CLL-001 was a phase 1, multicenter, open-label study that evaluated the safety and efficacy of lenalidomide administered orally by a stepwise dose-escalation schedule in subjects with relapsed or refractory B-cell CLL. Originally, this study was a multicenter, randomized, double-blind, parallel-group study designed to evaluate the efficacy and safety of two different dose regimens of lenalidomide in subjects with relapsed or refractory B-cell CLL. Subjects were randomized (1:1) in a double-blind fashion to receive lenalidomide 25 mg orally once daily on Days 1 to 21 of each 28-day cycle or lenalidomide 10 mg orally once daily continuously for 28 days of each 28-day cycle. Due to the occurrence of TLS combined in the more severe cases with TFR observed in 4 of the first 18 subjects enrolled, Celgene temporarily suspended study enrollment and convened an independent DMC to review the data. The DMC recommended that the study continue with modifications to define a better tolerated dosing regimen.

Subjects were to undergo screening assessments for protocol eligibility within 28 days of enrollment. Eligible subjects must have had CLL that had relapsed after or was refractory to at least one prior

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treatment regimen. Prior treatment must have included an alkylating agent (for example, chlorambucil or cyclophosphamide) and fludarabine (either sequentially or in combination). Subjects must have developed disease progression either during fludarabine-containing treatment or within 12 months of completing their most recent fludarabine-containing regimen (as measured from the completion of the last treatment cycle). Subjects with a history of prior alemtuzumab therapy must have received their last alemtuzumab dose at least 56 days prior to the initiation of lenalidomide treatment. Subjects meeting all eligibility criteria were to be enrolled into the study.

In this study, the tolerability of a stepwise dose-escalation schedule of lenalidomide administered by a daily regimen without rest periods was to be determined (Figure 1). The starting dose of lenalidomide for all subjects was 2.5 mg once daily. Escalation of the lenalidomide dose in an individual subject was not to occur more often than every 28 days. Subjects were to be enrolled until 6 subjects completed each cohort (until the maximum tolerated escalation dose level (MTEDL) was reached).

Figure 1: Study Design and Schedule of Assessments

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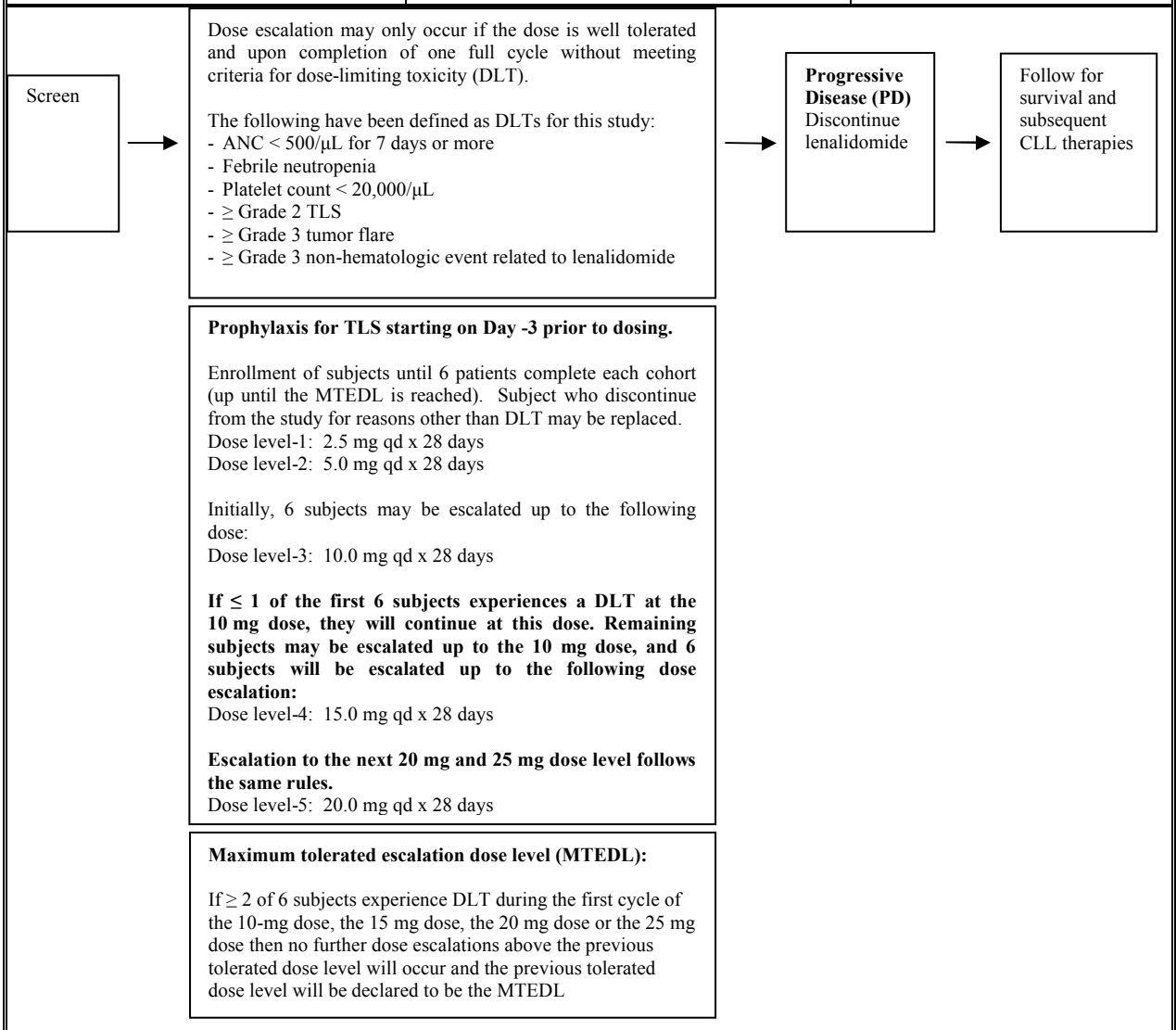

Dose escalation could only occur when subjects completed one cycle without meeting criteria for dose-limiting toxicity (DLT) (see definition below).

The following were defined as DLTs for this study:

- Absolute neutrophil count (ANC) < 500/µL for 7 days or more.
- Febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000/µL).
- Platelet count < 20,000/µL.
- ≥ Grade 2 TLS.

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- ≥ Grade 3 tumor flare.
- ≥ Grade 3 non-hematologic events determined by the Investigator to be related to lenalidomide (with the exception of thrombotic events).
  - For nausea, vomiting, or diarrhea, subjects must have a Grade 3 or 4 event that persists at this level despite the use of optimal symptomatic treatment, in order for these events to be considered a DLT.
  - Grade 4 transaminitis (serum transaminase > 20 x upper limit of normal [ULN]) is a DLT, while Grade 3 transaminitis (serum transaminase > 5 x and ≤ 20 x ULN) must be present for ≥ 7 days to be considered a DLT.
  - Grade 3 or 4 venous thromboembolic events are not considered to be DLTs as long as anticoagulant therapy can be administered.

Study visits and serial measurements of safety and efficacy for all subjects enrolled were to be performed as outlined in the schedule of assessments (Study CC-5013-CLL-001 Table 4). Subjects could continue receiving study drug until disease progression or unacceptable toxicity. Subjects who were discontinued from further study treatment were to be followed for overall survival and subsequent CLL treatment regimens.

During the screening process for potentially protocol-eligible subjects, a medical history, CBCs, serum chemistries, β2M test, thyroid function tests, quantitative immunoglobulin tests, cytokine assays, urinalysis, a 12-lead electrocardiogram (ECG), vital signs and a physical examination to assess lymphadenopathy, the spleen and the liver were to be performed. Bone marrow biopsies and aspirates and a peripheral blood draw were to be performed on all subjects at screening. A central review of the peripheral blood smears, bone marrow aspirate smears and bone marrow biopsies were to be performed to confirm disease status; however, local hematopathology results were used to verify eligibility requirements for enrollment into the study. Peripheral blood samples were also to be used for FISH studies for cytogenetic assessment, ZAP 70, mutational status studies, flow cytometry, and storage. A computed tomography (CT) scan of the neck, chest, abdomen and pelvis was to be performed for all subjects at screening, at the nodular partial remission (nPR) and CR confirmation visits, and at the treatment discontinuation visit for all subjects who discontinued except for those who discontinued due to PD.

Local laboratories at the clinical sites analyzed CBCs, serum chemistries, thyroid function tests and quantitative serum immunoglobulin assays for subjects enrolled in the study post Protocol Amendment 2. Local hematology tests were performed for all treatment-related decisions.

For all subjects, there was to be a central review of baseline and follow-up peripheral blood smears, bone marrow aspirate smears, and bone marrow biopsies (performed at baseline and at the time of CR confirmation visit) to assess disease status. A central laboratory, either in the US or EU, conducted FISH studies for cytogenetic assessment, ZAP 70 tests, mutational status studies, β2M analyses, and flow cytometry studies collected for MRD assessment.

An independent DMC reviewed ongoing safety and efficacy data on an ad hoc basis.

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Ongoing subjects

For ongoing subjects enrolled prior to Protocol Amendment 2, the treatment was unblinded at the time of Amendment 2 activation. The ongoing subjects were able to continue treatment at their current dose level at the time of unblinding, as tolerated. Re-escalation for these ongoing subjects was allowed in a stepwise manner up to the maximum dose (10 mg or 25 mg) to which they were originally randomized at time of their enrollment. Once Amendment 2 was activated, ongoing subjects followed a continuous dosing regimen (28 days of each 28 day cycle) regardless of which arm they were originally assigned to under the Original or Amendment 1 protocol. The results of this study were presented separately for the subjects enrolled under prior to Protocol Amendment 2 (Original subjects) and for the subjects enrolled after the implementation of Amendment 2 (Phase 1 subjects).

Number of patients (planned and analyzed):

Original (phase 2/3 study prior to the implementation of Protocol Amendment 2) – planned, 310 subjects; analyzed, 18 subjects

Phase 1 (per final protocol) – planned, approximately 50 subjects; analyzed, 52 subjects

Diagnosis and main criteria for inclusion:

Diagnosis: Relapsed or refractory B-cell CLL

Main criteria for inclusion:

- Aged ≥ 18 years at the time of signing the informed consent form.
- Documented diagnosis of B-cell CLL (The National Cancer Institute-Sponsored Working Group [NCI-WG] Guidelines for CLL, Response Criteria [1996]) that had relapsed after or was refractory to at least one prior regimen. The prior treatment regimen(s) must have included an alkylating agent (e.g., chlorambucil or cyclophosphamide) and fludarabine. Subjects must have developed disease progression either during or within 12 months of their most recent fludarabine-containing regimen.
- Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2.
- All subjects must have had an understanding that the study drug could have a potential teratogenic risk and therefore must have agreed to abstain from donating blood while on and following discontinuation of study drug therapy or sharing study medication with another person. In addition, all subjects were counseled about pregnancy precautions and the risks of fetal exposure (see specifics in Appendix 16.1.1).

Main criteria for exclusion:

- Any serious medical condition, laboratory abnormality, or psychiatric illness that prevented the subject from signing the informed consent form.
- Pregnant or lactating females.
- Systemic treatment for B-cell CLL within 28 days of initiation of lenalidomide treatment.
- Subjects with central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging and subjects with signs or symptoms of leukemic meningitis or a history of leukemic meningitis must have had a negative lumbar puncture within 2 weeks prior to randomization.

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- Prior history of malignancy other than CLL (except basal cell or squamous cell carcinoma or carcinoma in situ of the cervix or breast) unless the subject had been free of disease for ≥ 3 years.
- History of renal failure requiring dialysis.
- Known HIV-1 positivity.
- Prior therapy with lenalidomide.
- Alemtuzumab therapy within 56 days of initiation of lenalidomide treatment.
- Evidence of TLS per the Cairo-Bishop definition of laboratory TLS (Appendix 16.1.1) (subjects may have been enrolled upon correction of electrolyte abnormalities)
- Any of the following laboratory abnormalities:
  - ANC < 1000/µL (1.0 X 10P9P/L).
  - Platelet count < 50,000/µL (50 x 10P9P/L).
  - Calculated (method of Cockroft-Gault) creatinine clearance of < 60 mL/min.
  - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x ULN.
  - Serum total bilirubin > 2.0 mg/dL.
- Prior allergic reaction to thalidomide.
- Prior desquamating (blistering) rash while taking thalidomide.
- ≥ Grade 2 neuropathy.
- Uncontrolled autoimmune hemolytic anemia or thrombocytopenia.
- Richter's Transformation (active).

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

Celgene Corporation supplied 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg lenalidomide capsules for oral administration. Lenalidomide was packaged in bottles containing 28 capsules sufficient for 28 days of dosing. Each capsule of lenalidomide had the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The lenalidomide capsules were manufactured by or and packaged and labeled by . The lenalidomide clinical supplies were taken from the following batches/lot numbers: 06F0085, 06F0138, 07F0181, 07F0186, 07F0187, 07F0188, 07F0189, 07F0190, 07F0191, 07F0192, 07F0193, 07F0194, 07F0195, 07F0196, 07F0197, 07F0198, 07F0199, 07F0200, 07F0201, 07F0202, 07F0203, 07F0204, 07F0205, 07F0236, 07F027, 07F0238, 07F0242, 07F0243, 07F0244, 07F0247, 07F0248, 07F0252, 07F0253, 07F0254, 07F0255 08F0151, 08F0152, 08F0153, 08F0201, 08F0202, 08F0203, 08F0204, 08F0205, 08F0206, and 09F0100. Batches/lot numbers 10F0018, 10F0019, 10F0020, 10F0021, 10F0022, and 10F0023 were also allocated to this study, but were not taken by any of the subjects enrolled.

In the United States and Canada, commercial supplies of allopurinol were utilized for prophylaxis of TLS. For European centers, Celgene provided commercial supplies of allopurinol 300 mg labeled

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appropriately for investigational use to be utilized for prophylaxis of TLS.

Duration of treatment:

Subjects could receive study treatment until documented disease progression or unacceptable toxicity developed.

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

None

Criteria for evaluation:

Efficacy:

Response, duration of response, time to response, progression-free survival (PFS), overall survival, absolute lymphocyte count (ALC), evaluation of minimal residual disease (MRD) by flow cytometry

Safety:

Type, frequency, and severity of adverse events (AEs) and laboratory abnormalities and the relationship of AEs to lenalidomide

Statistical methods:

The maximum tolerated dose escalation level was not reached at 20 mg/daily and the protocol allowed for a validation of the 25 mg/daily dose escalation level. However, an administrative decision was made to end the study without the MTEDL having been reached, and not continuing enrollment to validate the 25 mg/daily dose level. In conjunction, an administrative decision was made to close the study after 25 Feb 2010 because the timepoint/events required for the primary and secondary analyses were reached:

- Primary analysis was to be performed after all subjects had completed at least 6 months of the study or had been discontinued from the study.
- A second analysis was to be performed and reported when 80% of all subjects had developed PD or died.

Subjects ongoing in the study at the time of study closure were transferred to the Celgene Patient Assistance Program and were able to continue treatment with commercial REVLIMID® at no cost.

The statistical analysis was descriptive in nature and was to account for all of the lenalidomide doses studied. Safety (type, frequency, and severity of AEs and relationship of AEs to lenalidomide) was summarized. Clinical response to treatment was also examined.

The baseline characteristics of subjects enrolled were summarized. An accounting was made of the study course for all subjects who received study drug and, in particular, the number of subjects who died or withdrew during treatment was specified and reasons for withdrawal categorized. Study drug administration was summarized.

Efficacy analysis was performed on the intent-to-treat (ITT) population that included all subjects enrolled. Confirmatory efficacy analysis was to be performed on the modified intent-to-treat (MITT) population and for relevant subgroups. Since the MITT population was the same as the ITT population, only one set of analyses was done.

Response rates together with confidence intervals were provided.

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Analyses were to be performed to characterize overall survival, PFS, duration of response, time to response and evaluation of MRD. The Kaplan-Meier procedure was to be used to characterize the time-to-event curves in these analyses when there was censoring. Otherwise, summary statistics (mean, standard deviation, median, minimum and maximum) were to be provided.

For both the Original and Phase 1 subjects, efficacy analysis was performed for PFS, response, and time to response. Duration of response, overall survival, ALC, and evaluation of MRD by flow cytometry was not be performed due to the small number of subjects enrolled in the phase 2/3 Original study and the limited efficacy observed in the Phase 1 study.

All subjects who received at least one dose of study medication were included in the safety analyses. Adverse events, vital sign measurements, clinical laboratory information, and concomitant medications were tabulated and summarized. Subject incidence rates of all AEs (including serious, Grade 3, Grade 4, treatment-related [with and without discontinuation] and events requiring the discontinuation of investigational product), were tabulated by system class, preferred term, and severity using Medical Dictionary for Regulatory Activities (MedDRA) terms and NCI Common Toxicity Criteria (CTCAE) (NCI CTCAE), Version 3.0 severity Grades.

Death and clinically important AEs (including tumor flare, tumor lysis, and thrombosis) were also summarized.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The total number of subjects (N = 18) enrolled in the study prior to Protocol Amendment 2 (randomized to either 10 mg daily or 25 mg daily on Days 1 to 21 of a 28-day cycle) was too low to derive specific efficacy conclusions.

During the phase 1 portion (N = 52), where subjects followed a dose-escalating continuous daily regimen of lenalidomide starting at 2.5 mg/day, 6 subjects (11.5%) displayed partial remission, 30 subjects (57.7%) had stable disease, and 13 subjects (25.0%) progressed based upon Celgene's assessment (applying NCI-WG criteria); 3 subjects were not evaluable. Median PFS was 24.1 weeks (range: 0.3 – 91.1 weeks). The 6 subjects who responded had reached the following maximum doses: 10 mg/day (n = 3), 15 mg/day (n = 1), and 20 mg/day (n = 2) lenalidomide. For 16 (30.8%) subjects, 2.5 mg/day was the maximum dose reached, and 22 (42.3%) subjects were unable to escalate beyond 5 mg/day. Efficacy results based on the investigator's assessment were similar to those obtained by applying NCI-WG criteria (Celgene's assessment).

SAFETY RESULTS:

Based on the analysis of safety data, the following conclusions can be reached:

Overall, the incidence rates of AEs observed when lenalidomide was administered in a dose-escalating regimen starting at 2.5 mg were consistent with the known safety profile of lenalidomide and with those seen in subjects with relapsed/refractory CLL (Chanan-Khan, 2006; Ferrajoli, 2007).

For the Original subjects starting at a lenalidomide dose of either 10 mg daily or 25 mg on Days 1 to 21 of a 28-day cycle, the median average daily dose was 10.0 mg and the median duration of treatment was

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12.2 weeks. The majority of subjects discontinued due to adverse event (50.0%) or disease progression (22.2%).

For the Phase 1 subjects on a dose-escalating continuous daily regimen starting at 2.5 lenalidomide, the median average daily dose was 4.5 mg and the median duration of treatment was slightly longer at 13.6 weeks. For those subjects able per protocol to dose-escalate to 20 mg, the median duration of treatment at 20 mg was 15.5 weeks. The majority of Phase 1 subjects discontinued due to disease progression (36.5%) or adverse event (28.8%).

The most frequently reported study drug-related AEs in the Original subjects overall were neutropenia (44.4%), anemia (38.9%), thrombocytopenia (38.9%), febrile neutropenia (22.2%), tumor flare (55.6%), tumor lysis syndrome (27.8%), diarrhea (27.8%), and fatigue (44.4%). Similarly, neutropenia (59.6%), thrombocytopenia (50.0%), anemia (26.9%), and tumor flare (44.2%) were the most frequently reported study drug-related AEs in the Phase 1 subjects.

The incidence of TLS was decreased between the Original subjects (27.8%; Grade 3/4 in 2 subjects, Grade 5 in 1 subject) (Table 14.3.2.5.3) and the Phase 1 subjects (3.8%; 1 subject with Grade 2 TLS and 1 subject with laboratory TLS; both at 2.5 mg/day) (Listing 16.2.7.1A), suggesting that TLS can be prevented and managed. However, further investigation is warranted to determine if this is primarily attributable to the titration of the lenalidomide dose or to the implementation of appropriate monitoring and prophylaxis for TLS.

CONCLUSION:

The results of this phase 1, multi-center, open-label study demonstrate that lenalidomide, when administered at a starting dose of 2.5 mg daily in a dose-escalating regimen, has a manageable safety profile in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia.

Overall, the most frequently reported study drug-related AEs in this study were neutropenia, thrombocytopenia, anemia, and tumor flare. The rates of SAEs or discontinuations due to neutropenia, thrombocytopenia, anemia or tumor flare suggest that these most frequently observed AEs were manageable with dose reductions or interruptions and with appropriate monitoring and supportive care.

The incidence of TLS was decreased between the Original subjects (27.8%; Grade 3/4 in 2 subjects, Grade 5 in 1 subject) (Table 14.3.2.5.3) and the Phase 1 subjects (3.8%; 1 subject with Grade 2 TLS and 1 subject with laboratory TLS; both at 2.5 mg/day) (Listing 16.2.7.1A), suggesting that TLS can be prevented and managed. However, further investigation is warranted to determine if this is primarily attributable to the titration of the lenalidomide dose or to the implementation of appropriate monitoring and prophylaxis for TLS.

Of the Phase 1 subjects, 6 subjects (11.5%) displayed a partial response, 30 subjects (57.7%) had stable disease, and 13 subjects (25.0%) progressed based upon Celgene's assessment (applying NCI-WG criteria); 3 subjects were not evaluable. Median progression-free survival was 24.1 weeks (range: 0.3 – 91.1 weeks). The 6 subjects who responded had reached the following maximum doses: 10 mg/day (n = 3), 15 mg/day (n = 1), and 20 mg/day (n = 2) lenalidomide. For 16 (30.8%) subjects, 2.5 mg/day was the maximum dose reached, and 22 (42.3%) subjects were unable to escalate beyond 5 mg/day. Based on this data, a higher starting dose of lenalidomide, as previously reported by Chanan-Khan et al. (2006) and Ferrajoli et al. (2008), may be needed for relapsed/refractory CLL patients to achieve greater

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clinical efficacy. Date of the report: 30 Sep 2010		