FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (IDELA)
Dose and Formulation:	IDELA 150 mg or placebo tablets, twice daily
Indication:	Chronic Lymphocytic Leukemia (CLL)
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA
Study No.:	GS-US-312-0116
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	101254 2011-005180-24
Study Start Date:	01 May 2012 (First Subject Randomized)
Study End Date:	20 April 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Jeff Sharman, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Thomas M. Jahn, MD, PhD Telephone: PPD Fax: PPD
Report Date:	25 November 2014

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-312-0116

Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102
USA

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Investigators: This study was a multicenter study.

Study Centers: A total of 53 sites in the United States (US), France, United Kingdom, Italy, and Germany enrolled subjects for this study.

Publications:

Coutre SE, Furman RR, Sharman JP, Cheson BD, Pagel JM, Hillmen P, et al. Second Interim Analysis of a Phase 3 Study Evaluating Idelalisib and Rituximab for Relapsed CLL [Poster 7012]. American Society of Clinical Oncology (ASCO) 50th Annual Meeting; 2014 May 30-June 3; Chicago, IL.

Coutre SE, Furman RR, Sharman JP, Cheson BD, Pagel JM, Hillmen P, et al. Second Interim Analysis of a Phase 3 Study Evaluating Idelalisib and Rituximab for Relapsed CLL [Abstract ABSSUB-4736-S704]. European Hematology Association (EHA) 19th Congress; 2014 June 12-15; Milan, Italy.

Eradat HA, Ghia P, O'Brien SM, Hillmen P, Furman RR, Coutre SE, et al. Health-Related Quality of Life Impact of Idelalisib (IDELA) in Patients with Relapsed Chronic Lymphocytic Leukemia (CLL): Phase 3 Results [Abstract ABSSUB-4637- P252]. European Hematology Association (EHA) 19th Congress; 2014 June 12-15; Milan, Italy.

Eradat HA, Robak T, Delgado J, Schuh A, Pristupa AS, Omyla-Staszewska J, et al. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukemia (CLL) [Poster 7127] American Society of Clinical Oncology (ASCO) 50th Annual Meeting; 2014 May 30-June 3; Chicago, IL.

Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2014;370 (11):997-1007.

Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib and Rituximab for Previously Treated Patients with Chronic Lymphocytic Leukemia (CLL) [Abstract LBA-6]. American Society of Hematology Meeting and Exposition, 2013 December 7-10; New Orleans, LA.

Ghia P, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Effect of Idelalisib/Rituximab Combination Treatment of Relapses CLL on the BCR Signaling-Related Chemokines CCL3 and CCL4: Data from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial [Abstract ABSSUB-4754-P239]. European Hematology Association (EHA) 19th Congress; 2014 June 12-15; Milan, Italy.

Ghia P, O'Brien SM, Hillmen P, Furman RR, Coutre SE, Sharman JP, et al. Health-related Quality of Life (HRQL) Impact of Idelalisib in Patients with Relapsed Chronic Lymphocytic Leukemia: Phase 3 Results [Poster 7099]. American Society of Clinical Oncology (ASCO) 50th Annual Meeting; 2014 May 30-June 3; Chicago, IL.

Hillmen P, Furman RR, Coutre SE, Sharman JP, Pagel JM, Barrientos JC, et al. Pre-Treatment with Idelalisib Markedly Reduces Rituximab Infusion-Related Reactions and Infusion Interruptions in Patients with CLL [Abstract ABSSUB-4810-P236]. European Hematology Association (EHA) 19th Congress; 2014 June 12-15; Milan, Italy.

Sharman JP, Coutre SE, Furman FF, Cheson BD, Pagel JM, Hillmen P, et al. Efficacy of Idelalisib in CLL Subpopulations Harboring Del(17p) and Other Adverse Prognostic Factors: Results from a Phase 3, Randomized, Double-blind, Placebo-controlled Trial [Poster 7011]. American Society of Clinical Oncology (ASCO) 50th Annual Meeting; 2014 May 30-June 3; Chicago, IL.

Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors [Session 642 Abstract 330]. American Society of Hematology (ASH) 56th Annual Meeting; 2014 December 6-9; San Francisco, CA.

Stilgenbauer S, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Efficacy of idelalisib in CLL Subpopulations Harboring Del(17p) and Other Adverse Prognostic Factors: Results from a Phase 3, Randomized, Double-Blind Placebo-Controlled Trial [Abstract ABSSUB-4694 S1341]. European Hematology Association (EHA) 19th Congress; 2014 June 12-15; Milan, Italy.

Study Period:

01 May 2012 (First Subject Randomized)
20 April 2014 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was:

- To evaluate the effect of the addition of IDELA to rituximab on progression-free survival (PFS) in subjects with previously treated CLL

The secondary objectives of this study were:

- To evaluate the effect of the addition of IDELA to rituximab on the onset, magnitude, and duration of tumor control
- To assess the effect of the addition of IDELA to rituximab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status
- To assess the effects of the addition of IDELA to rituximab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to IDELA
- To characterize the effect of rituximab on IDELA exposure through evaluations of IDELA plasma concentrations over time
- To describe the safety profile observed with the addition of IDELA to rituximab
- To estimate health resource utilization associated with the addition of IDELA to rituximab

Methodology: Study GS-US-312-0116 was a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled study conducted at centers in the US and Europe.

Randomization was stratified by17p deletion and/or a *TP53* mutation status (either versus neither [or indeterminate]), immunoglobulin heavy chain variable region [*IGHV*] mutation status (unmutated [or *IGHV*3-21] versus mutated [or indeterminate]), and any prior therapy with an anti-CD20 therapeutic monoclonal antibody (yes versus no) and in a 1:1 ratio to receive 1 of 2 treatments.

Subjects in Arm A received IDELA + rituximab (IDELA + R), and subjects in Arm B received placebo + rituximab (placebo + R).

Rituximab was administered intravenously in the clinic starting at a dose of 375 mg/m^2 on Day 1 (Week 0); thereafter at 500 mg/m^2 intravenously on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16) and Day 141 (Week 20) for a total of 8 infusions. IDELA or placebo was taken orally, twice daily on Day 1 and continuously thereafter.

The study included 2 prespecified formal interim efficacy analyses to be evaluated by an independent Data Monitoring Committee (DMC). Based on results from the first interim efficacy analysis, the DMC recommended stopping the trial for overwhelming efficacy, and Gilead agreed. On 07 October 2013, a decision was made in consultation with the US Food and Drug Administration (FDA) to stop the study early and to perform a second interim analysis on blinded data up to 09 October 2013. The database for the blinded portion of the study was finalized 08 November 2013 and the study was unblinded on that date. This report summarizes results from the final analysis of data up to the date of the last subject observation for subjects who received IDELA + R (20 April 2014) and data up to the first dosing of open-label IDELA for subjects who received placebo + R.

Number of Subjects (Planned and Analyzed):

Planned: approximately 200 subjects (approximately 100 per treatment arm)
Analyzed: 220 subjects (110 subjects each: IDELA + R and placebo + R)

Diagnosis and Main Criteria for Inclusion:

Target Population: Adult subjects with previously treated recurrent CLL who had measurable lymphadenopathy, required therapy for CLL, had experienced CLL progression < 24 months since the completion of the last prior therapy, and were not fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities.

1) Diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records
2) CLL that warranted treatment (consistent with accepted IWCLL criteria for initiation of therapy).
3) Presence of radiographically measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measured ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI])
4) Prior treatment for CLL comprising either of the following:
    - Prior treatment with ≥ 1 regimen containing a therapeutic anti-CD20 antibody administered for ≥ 2 doses of antibody treatment
    - Prior treatment with ≥ 2 regimens containing ≥ 1 cytotoxic agent administered for ≥ 2 cycles of cytotoxic treatment
5) In a subject whose last prior therapy contained an anti-CD20 antibody (eg, rituximab, ofatumumab, GA-101 [obinutuzumab]), evidence of disease improvement during that therapy or documentation of CLL progression ≥ 6 months after completion of that therapy
6) Documentation of CLL progression < 24 months since the completion of the last prior therapy for CLL
7) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥ 3 weeks before randomization
8) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grades 1, 2, 3, or 4 permitted])
9) Karnofsky performance score of ≥ 40

Duration of Treatment: Study drug (IDELA/placebo) was taken continuously until the earliest of subject withdrawal from study drug, definitive progression of CLL, study drug-related toxicity, pregnancy, noncompliance with study procedures, or study discontinuation.

Rituximab was administered until the earliest of a maximum of 8 infusions, subject withdrawal from study, definitive progression of CLL, rituximab-related toxicity, pregnancy, noncompliance with study procedures, or study discontinuation.

Study GS-US-312-0117 is a separate, multicenter, 2-arm, double-blind, parallel-group extension trial that is a companion trial to Study GS-US-312-0116; in this trial, compliant subjects from GS-US-312-0116 who were tolerating primary study therapy but experienced definitive CLL progression were eligible to receive active blinded IDELA therapy at the standard dose or a higher dose, with allocation based on the original primary study randomization.

When Study GS-US-312-0116 was stopped early due to efficacy, subjects were eligible to transition to GS-US-312-0117. Consequently, GS-US-312-0117 became an open-label study offering IDELA 150 mg twice daily to GS-US-312-0116 subjects. Subjects could continue receiving IDELA and rituximab in Study GS-US-312-0116 until transition onto the extension study was possible.

Test Product, Dose, Mode of Administration, and Lot No.:

IDELA: 150 mg taken orally twice daily starting on Day 1 and taken continuously thereafter
Lot No.: CV1104D1, CY1202B1, CV1204B1, CY1206B1
Dose reductions to 100 mg taken orally twice daily
Lot No.: CV1104C1,CY1201B1

Placebo: 150 mg taken orally twice daily starting on Day 1 and taken continuously thereafter
Lot No.: CV1108D1, CV1203B1

Reference Therapy, Dose, Mode of Administration, and Lot No.:

Rituximab: 375 mg/m^2 administered intravenously on Day 1 (Week 0);
thereafter 500 mg/m^2 administered intravenously on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), Day 141 (Week 20) (for a total of 8 infusions)

Criteria for Evaluation:

Efficacy:

Primary Endpoint

- PFS – defined as the interval from randomization to the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria, other than lymphocytosis alone.

Secondary and Tertiary Endpoints

Four endpoints were designated as secondary endpoints: Overall response rate (ORR), lymph node response (LNR) rate, OS, and complete response (CR) rate. All other endpoints were considered tertiary.

Disease Control

- ORR – defined as the proportion of subjects who achieve a CR or partial response (PR)
- LNR rate – defined as the proportion of subjects who achieve a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes

- OS – defined as the interval from randomization to death from any cause
- CR rate – defined as the proportion of subjects who achieve a CR
- Time to response (TTR) – defined as the interval from randomization to the first documentation of CR or PR
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause
- Percent change in lymph node area – defined as the percent change from baseline in the SPD of index lesions
- Splenomegaly response rate – defined as the proportion of subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or decrease to $\leq$ 12 cm by imaging
- Hepatomegaly response rate – defined as the proportion of subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the liver in its LVD or decrease to $\leq$ 18 cm by imaging
- Absolute lymphocyte count (ALC) response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC $\geq 4 \times 10^9$/L) who achieve an on-study ALC $< 4 \times 10^9$/L or demonstrate a $\geq$ 50% decrease in ALC from baseline. ALC values within 4 weeks post-baseline were excluded from the ALC response rate evaluation.
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count $< 100 \times 10^9$/L) who achieve an on-study platelet count $\geq 100 \times 10^9$/L or demonstrate a $\geq$ 50% increase in platelet count from baseline. Platelet values within 4 weeks post-baseline were excluded from the platelet response rate evaluation. Any platelet responses within 8 days of platelet transfusion were excluded from the platelet response rate evaluation.
- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin < 110 g/L [11.0 g/dL]) who achieve an on-study hemoglobin $\geq$ 110 g/L (11.0 g/dL) or demonstrate a $\geq$ 50% increase in hemoglobin from baseline. Hemoglobin values within 4 weeks post-baseline were excluded from the hemoglobin response rate evaluation. Hemoglobin responses achieved within 4 weeks of taking erythropoietin stimulating agents (ESAs) were excluded from the hemoglobin response rate evaluation.
- Absolute neutrophil count (ANC) response rate – defined as the proportion of subjects with baseline neutropenia (ANC $\leq 1.5 \times 10^9$/L) who achieve an ANC $> 1.5 \times 10^9$/L or demonstrate a $\geq$ 50% increase in ANC from baseline. ANC values within 4 weeks post-baseline, 2 weeks after G-CSF or other grow factors and 4 weeks after Neulasta were excluded from the ANC response rate evaluation.

Patient Well-Being

- Change from baseline in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu)
- Changes from baseline in Karnofsky performance status

- Changes from baseline in PI3K/AKT/mTOR pathway activation as a measure of PI3Kδ pathway activity
- Changes from baseline in the plasma concentrations of disease-associated chemokines and cytokines

Exposure

- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Trough (predose) and peak (1.5-hour samples) of IDELA plasma concentrations as assessed by a validated bioanalytical method

Safety

- Overall safety profile of each regimen characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study drug.

Pharmacoeconomics

- Change in health status – defined as the change from baseline in overall health and single-item dimension scores as assessed using the EuroQoL Five-Dimension (EQ-5D) utility measure
- Health resource measures, including resource utilization, total costs, and measures of cost per unit of benefit (eg, cost per additional progression-free month, cost per quality-adjusted life-year)

Statistical Methods:

Efficacy: An IRC was established for this study and included a pool of 5 radiologists. Each scan was read by 2 primary board-certified radiologists and a board-certified adjudicating radiologist, (when adjudication was needed) and an independent board-certified hematologist or oncologist performed an independent review of response and disease progression for each subject. The findings of the IRC were considered primary for analyses of PFS and other disease control endpoints.

Two interim analyses were prespecified at ~50% and ~75% of the planned 119 PFS events and were to be tested at a 2-sided significance level of 0.001 and 0.005, respectively. These analyses offered the opportunity to assess for evidence of substantial clinical benefit early. A decision was made to stop the blinded-phase of the study after the first interim analysis as the 2-sided p-value for the primary PFS analysis crossed the prespecified alpha boundary of 0.001. In accordance with the discussion with the FDA on 07 October 2013, Gilead conducted a second analysis of the blinded-phase based on a data cut-off date of 09 October 2013. The significance level of the second analysis was prespecified at 0.005 for the PFS endpoint and 0.05 for the secondary endpoints. A public announcement of stopping the trial due to overwhelming efficacy observed from the first interim analysis was made on 09 October 2013. Results presented herein reflect the final analysis of Study GS-US-312-0116.

The stratification factor, 'any prior therapy with anti-CD therapeutic antibody' status was highly skewed toward 'yes', with approximately 96% of subjects having had prior anti-CD20 therapy. Thus, this stratification factor was excluded from all stratified analyses that were prespecified in the study protocol and SAP and only 17p deletion and/or *TP53* mutation status and *IGHV* mutation status were considered.

Primary Endpoint:

The primary endpoint, PFS, was defined as the interval from randomization to the first documentation of definitive progressive disease (PD) or death from any cause; definitive disease progression was CLL progression based on standard criteria other than lymphocytosis alone. The statistical hypothesis for the primary endpoint was as follows: H_0: hazard ratio (between Arm A [IDELA + R] and Arm B [placebo + R]) equals 1 versus H_1: hazard ratio is less than 1. For the primary efficacy analysis, PFS between the 2 treatment arms was compared, based on the intent-to-treat (ITT) Analysis Set using a stratified log-rank test, adjusted for stratification factors. Hazard ratios and corresponding 95% CIs were obtained using a Cox proportional hazard regression model adjusting for stratification factors. The Kaplan-Meier (KM) plot for PFS by treatment arm was also provided.

Sensitivity analyses of PFS in support of the primary analysis were also performed, including: 1) analysis of PFS in the ITT Analysis Set using the unstratified log-rank test, 2) analysis of PFS in the per-protocol (PP) Analysis Set using the stratified log-rank test, and 3) analysis of PFS in the ITT Analysis Set using the stratified log-rank test by treating data from surviving, nonprogressing subjects in Arm A as events at the last time that lack of definitive CLL progression was objectively documented. In addition, subgroup analyses of PFS by 17p deletion and/or *TP53* mutation status, *IGHV* mutation status, 17p deletion status, gender, age, and race were also performed.

Secondary Endpoints:

Secondary efficacy endpoints included ORR, LNR rate, OS, and CR rate. Analysis of CR rate was not performed, as no subject achieved a CR.

Differences in number and percentage of subjects between the treatment arms in ORR were compared using CMH Chi-square tests after adjusting for stratification factors. Odds ratios and the corresponding 95% CIs were presented as well.

Differences in LNR rate between the 2 treatment arms were compared using CMH Chi-square tests after adjusting for stratification. Only subjects that had both baseline and at least 1 evaluable postbaseline SPD were included in this analysis.

The primary OS analysis was performed using the ITT Analysis Set (according to the original randomization) which included all available survival information from Study GS-US-312-0116 (including long-term follow-up data), and its companion Study GS-US-312-0117 (including long-term follow-up data up to the cutoff date of 01 July 2014). Data from surviving subjects were censored at the last time that the subject was known to be alive on study and long-term follow-up. Differences between the treatment arms in OS were assessed using a stratified log-rank tests, adjusted for stratification factors. Medians, Q1, Q3, hazard ratios and corresponding 95% CIs were presented by treatment arm. Plots of time to event by treatment arm were provided using the KM method.

Subgroups analyses of ORR and LNR rate by 17p deletion and/or *TP53* mutation status, *IGHV* mutation status, 17p deletion status, gender, age and race were also performed. In addition, analysis of ORR and LNR rate in the PP Analysis Set was performed.

Tertiary Endpoints:

TTR and DOR were assessed based on ITT subjects who achieved a CR or PR. Descriptive statistics were provided for TTR. DOR was summarized using KM methods.

The best percent change from baseline in SPD, splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate and ANC response rate were also summarized. For the summaries of response rates, only subjects who had relevant abnormality at baseline and at least 1 valid postbaseline value were included.

The Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) questionnaire included subscales for physical well-being, social/family well-being, emotional well-being, functional well-being, and Additional Concerns (Leukemia Subscale). Two composite scores, trial outcome index and FACT-Leu total scores, were derived from the subscale scores. Data were analyzed using appropriate methods specified in the user manual to account for incomplete completion of questionnaires. The mean and change from baseline to each subsequent assessment were summarized for the subscale and composite scores by treatment arms. The best change from baseline during the study was also summarized. A mixed effects model for longitudinal data was used to compare the 2 treatment arms. The model included fixed effect treatment, study weeks, treatment-by-study-week interactions, and stratification factors as covariates. The cumulative distribution function (CDF) of best change from baseline was provided.

The Karnofsky performance status scores and change from baseline scores to each subsequent assessment were summarized, in addition to the best changes from baseline during the study.

The EQ-5D questionnaire data were scored, processed, and standardized according to the user manual. The mean and change from baseline were summarized for the EQ-5D visual analogue scale (VAS) values. The proportion of subjects at levels 1, 2, and 3 of the 5 dimensions (ie, mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and by treatment arms were presented.

Exposure and Pharmacodynamics: IDELA plasma concentrations immediately predose and at 1.5 hours after administration of the dose of study drug at various clinic visits were summarized by treatment and visit using descriptive statistics. A separate biomarker analysis plan was prepared to detail pharmacodynamics and biomarker analyses.

Safety: Adverse events were classified by Medical Dictionary for Regulatory Activities, version 17. The severity of AEs was graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. The relationship of an AE to the component of study drug (IDELA/placebo) and rituximab and to the infusion of rituximab was assessed by the investigator, as either unrelated or related.

All AEs were listed, and treatment-emergent AEs were summarized. A treatment-emergent AE was defined as an AE that occurred or worsened in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study, or a continuing AE diagnosed prior to the start of treatment and worsening in severity grade after the start of treatment, a non-serious AE at baseline becoming serious after the start of treatment, or an AE resulting in treatment discontinuation after the start of treatment.

Listings and summaries were prepared for treatment-emergent AEs classified by severity (Grade 3 or higher); AEs reported as related to study drug by investigators; AEs leading to treatment interruption, modification, or discontinuation; and SAEs.

Incidence of AEs was summarized by time interval: 0 to 12 weeks, 12 to 24 weeks, and > 24 weeks, and exposure-adjusted AE rates were summarized for specific AEs of interest. Incidence of TEAEs in each interval is defined as the proportion of subjects with onset of TEAE in that interval among those at risk at the beginning of the interval.

Treatment-emergent laboratory abnormalities were summarized for hematological and serum biochemistry data. A treatment-emergent laboratory abnormality was defined as an abnormality that, compared to baseline, worsened by ≥ 1 grade in the period from the first dose of study drug to 30 days after the last dose of study drug. Shift tables for hematology and serum biochemistry were presented showing change in CTCAE severity grade from baseline to worst grade postbaseline. Exposure-adjusted laboratory abnormality rates were calculated. The exposure-adjusted treatment-emergent laboratory abnormality rate was defined as the number of subjects with a specific event divided by the total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the event.

SUMMARY OF RESULTS:

A decision was made to stop the blinded-phase of the study at the first interim analysis as the 2-sided p-value for the primary PFS analysis crossed the prespecified alpha boundary of 0.001. A second interim analysis of the blinded-phase data was performed based on a data cut-off date of 09 October 2013. The significance level of this second interim analysis was 0.005 for the PFS endpoint and 0.05 for the secondary endpoints. The blind was maintained between the first and second interim analyses. The results presented herein reflect the final analysis of Study GS-US-312-0116 (both blinded and unblinded phases).

Subject Disposition, Exposure, Demographics, and Baseline Characteristics:

Two hundred and twenty subjects were randomized in the study (110 per treatment group), of whom 218 received at least 1 dose of study drug (110 IDELA + R; 108 placebo +R). A total of 158 subjects (71.8%) discontinued study treatment prior to disease progression (IDELA + R: 91.8%, 101 subjects; placebo + R: 51.8%, 57 subjects) with the majority of these discontinuations due to completion of Study GS-US-312-0116 and crossover into the open-label IDELA study, GS-US-312-0117 (IDELA + R: 63.6%, 70 subjects; placebo + R: 35.5%, 39 subjects). In the IDELA + R group, 19 subjects (17.3%) discontinued due to AE, 10 subjects (9.1%) discontinued due to subject withdrawal, 1 subject (0.9%) discontinued due to physician decision, and 1 subject (0.9%) discontinued for “other” (Richter’s transformation) reasons. In the placebo + R group, 14 subjects (12.7%) discontinued due to AE, 3 subjects (2.7%) discontinued due to subject withdrawal, and 1 subject (0.9%) discontinued due to physician decision. The median duration of exposure to study drug was 8.1 months for subjects receiving IDELA + R and 4.6 months for subjects receiving placebo + R.

Overall, demographic and baseline characteristics (age, gender, race, BMI) were generally comparable between the groups. Consistent with the advanced age typical of the general CLL population and the inclusion criteria for this study, most subjects (78.2%) were ≥ 65 years of age, with a median (Q1, Q3) age of 71 (66, 76) years, and an age range of 47 to 92 years. Most subjects (65.5%) were male, white (90.0%), and not Hispanic or Latino (92.7%). The median (Q1, Q3) baseline BMI was 25.3 (23.0, 29.0) kg/m^2.

Baseline disease characteristics reflect the advanced stage of CLL and poor prognostic factors present in the study population. The median (Q1, Q3) time since diagnosis was 8.5 years (5.5, 12.0) (102.0 months [65.8, 143.9]), and most subjects had advanced disease at screening, with 64.1% Rai Stage III or IV and 55.9% Binet Stage C. Approximately half of the 220 study subjects had presence of either 17p deletion and/or *TP53* mutation (43.2%), and most subjects had unmutated *IGHV* status (83.6%). A total of 149 subjects (67.7%) had splenomegaly and 117 subjects (53.2%) had hepatomegaly at baseline. Almost all subjects (192 subjects; 87.3%) had a reduced KPS at study entry: 63.1% had modest reduction (ie, KPS scores of 80 and 90), 20.0% had significant reduction (ie, KPS scores of 60 and 70), and approximately 4.1% had severe impact (ie, KPS score ≤ 50).

Most subjects (85.0%) had renal dysfunction as indicated by estimated creatinine clearance (eCL_{cr}) (Cockcroft-Gault method) of < 90 mL/min, and the median (Q1, Q3) eCL_{cr} was 63.6 (53.4, 79.8) mL/min. Eighty-seven subjects (39.5%) had eCL_{cr} of 30 to < 60 mL/min (ie, moderate renal impairment), and 99 subjects (45.0%) had eCL_{cr} of 60 to < 90 mL/min (ie, mild renal impairment).

The median (Q1, Q3) Cumulative Illness Rating Scale (CIRS) score was 8.0 (7.0, 10.0; range 1.0 to 18.0), demonstrating that the study comprised a population with significant non-disease related comorbidities. Most subjects (188 subjects, 85.5%) had CIRS scores of > 6. Comorbidities were common across organ systems. For example, 36.8% of subjects had cardiac comorbidities, 41.8% of subjects had endocrine/metabolic comorbidities, 39.5% had renal comorbidities, and 51.8% had respiratory comorbidities. A total of 208 subjects (94.5%) had 3 or more organs with comorbidities and 82 subjects (37.3%) had severe comorbidities (score of 3 or higher in any system). CIRS scores were comparable between treatment groups. In addition, 47.7%, 80.9%, and 25.5% of the total study population had abnormally low platelet count, hemoglobin, and ANC, respectively. These hematologic results were balanced across treatment groups at baseline.

The study population was heavily pretreated for CLL. The median (Q1, Q3) number of prior CLL regimens was 3 (2, 5), with a range of 1 to 12 prior regimens received. The most common prior regimens were bendamustine + R (98 subjects, 44.5%), fludarabine + cyclophosphamide + R (75 subjects, 34.1%), single-agent rituximab (67 subjects, 30.5%), fludarabine + R (38 subjects, 17.3%), and chlorambucil (36 subjects, 16.4%). Of note, a wide array of treatments were administered as the last treatment prior to study; 46 unique treatment regimens were identified, including 8 regimens containing at least 1 investigational agent.

In summary, the study population consisted of elderly, frail subjects with relapsed or refractory CLL who had multiple prior therapies and lacked standard treatment options.

Efficacy Results: Final efficacy results of the study were consistent with the first and second interim analyses, and overwhelmingly support the use of IDELA in combination with rituximab for previously treated CLL in older, frail patients with comorbidities that prevent use of cytotoxic chemotherapy.

Primary Endpoint

Progression-Free Survival: Analysis of PFS as assessed by the IRC based on the ITT Analysis Set and stratified by 17p deletion and/or *TP53* mutation status and *IGHV* mutation status showed superiority of IDELA + R compared with placebo + R, with an adjusted

hazard ratio (95% CI) of 0.15 (0.09, 0.24) and 2-sided p-value of 1.6×10^{-16} based on a stratified log-rank test. A total of 25 subjects (22.7%) in the IDELA + R group and 70 subjects (63.6%) in the placebo + R group experienced a PFS event. The median (95% CI) PFS for subjects in the IDELA + R group was 19.4 (12.3, not reached [NR] months. In comparison, the median (95% CI) PFS for subjects in the placebo + R group was 6.5 (4.0, 7.3) months. Results of PFS analyses were consistently in favor of IDELA + R compared with placebo + R across all predefined subgroups and in all prespecified sensitivity analyses.

It is most notable that the treatment effect of IDELA + R was equally profound in the adverse genetics subgroups of 17p deletion (unadjusted hazard ratio [95% CI] of 0.14 [0.05, 0.34]), 17p deletion or *TP53* mutation (unadjusted hazard ratio [95% CI] of 0.13 (0.07, 0.27]) and unmutated *IGHV* (unadjusted hazard ratio [95% CI] of 0.14 [0.08, 0.23]). The median (95% CI) PFS for the IDELA + R group compared with the placebo + R group for subjects with 17p deletion was NR (9.2 months, NR) versus 3.7 months (1.9, 5.5), respectively; for subjects with 17p deletion or *TP53* mutation was NR (12.3 months, NR) versus 4.0 months (3.7, 5.7), respectively; and for subjects with unmutated *IGHV* was 19.4 months (13.9, NR) versus 5.6 months (4.0, 7.2), respectively.

Secondary Endpoints

Overall Response Rate: Based on the ITT Analysis Set, the ORR (classified as CR or PR) (95% CI) for subjects in the IDELA + R group was 83.6% (75.4, 90.0), and the ORR (95% CI) for subjects in the placebo + R group was 15.5% (9.3, 23.6). The odds ratio (95% CI) for the ORR was 27.76 (13.40, 57.49), which favored IDELA + R compared with placebo + R (p-value = 1.3×10^{-23}). Results of ORR analyses were also consistently in favor of IDELA + R compared with placebo + R in the sensitivity analysis based on the PP Analysis Set and across all predefined subgroups. No CRs were observed in either arm.

Lymph Node Response Rate: The stratified odds ratio (95% CI) for the LNR rate was 225.83 (65.56, 777.94), which overwhelmingly favored IDELA + R compared with placebo + R (p-value = 8.5×10^{-38}). The LNR rate (95% CI) for subjects in the IDELA + R group was 96.2% (90.6, 99.0), and for subjects in the placebo + R group, the LNR rate (95% CI) was 6.7% (2.7, 13.4). LNR rate results favored IDELA + R over placebo + R across all subgroups.

Overall Survival: The primary OS analysis was performed using the ITT Analysis Set (according to the original randomization) which included all available survival information from Study GS-US-312-0116 (including long-term follow-up data) and its companion Study GS-US-312-0117 (including long-term follow-up data up to the cutoff date of 01 July 2014). A total of 57 subjects died (IDELA + R: 17 subjects; 15.5%; placebo + R: 40 subjects, 36.4%). IDELA + R demonstrated a statistically significant improvement in OS. The adjusted hazard ratio (95% CI) for OS was 0.34 (0.19, 0.60), with a p-value from stratified log-rank test of 0.0001.

A sensitivity analysis was performed, censoring OS for the placebo + R group at the time of crossover to IDELA. The adjusted hazard ratio (95% CI) for this sensitivity analysis was 0.43 (0.20, 0.95) with a p-value from stratified log-rank test = 0.0332.

Tertiary Endpoints

Time to Response: Among subjects who achieved a response (CR or PR), the median (Q1, Q3) TTR was 2.1 months (1.9, 3.7) for subjects treated with IDELA + R (N = 92) and 2.8 months (2.0, 3.9) for subjects treated with placebo + R (N = 17).

Duration of Response: Among subjects who achieved a response (CR or PR), the median (Q1, Q3) DOR was NR (10.4 months, NR) for subjects treated with IDELA + R (N = 92) and 6.2 (4.0, 6.5) months for subjects treated with placebo + R (N = 17).

Best Percent Change in SPD: The best percent change in SPD was assessed among the subjects in each treatment group with measurable index lesions at both baseline and postbaseline. The median (Q1, Q3) best percent change in SPD was -76.8 (-82.9, -68.7) for subjects treated with IDELA + R (N = 106) and -6.9 (-25.4, 7.8) for subjects treated with placebo + R (N = 104). The interquartile ranges did not overlap and the best percent change in SPD favored IDELA + R over placebo + R across all subgroups.

Additional Response Rates: For analyses of additional efficacy endpoints, only subjects with corresponding abnormality at baseline and at least 1 valid postbaseline value were included. Hepatomegaly and splenomegaly response rates strongly favored IDELA + R (76.6% and 54.5%, respectively) compared with placebo + R (21.9% and 18.3%, respectively). The ALC, platelet, hemoglobin, and ANC response rates in the IDELA + R group were higher when compared with placebo + R: 92.0%, 93.8%, 78.0%, and 85.9% compared with 81.5%, 52.1%, 42.9%, and 69.2%, respectively.

HRQL: Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) Questionnaire Results: In both treatment arms, the mean postbaseline scores for the Additional Concerns (Leukemia), FACT-Leu Total, and the Trial Outcome Index scores were higher than baseline scores; however, subjects treated with IDELA + R consistently showed greater symptom improvement than subjects on placebo + R at each timepoint throughout the study. Subjects treated with IDELA + R reached the minimally important difference (MID) for Additional Concerns rapidly (Week 4) and their improvement was sustained, whereas subjects on placebo + R reached MID at Week 72. In the mixed-effects model analysis of the changes from baseline in the Additional Concerns subscale score, the main effect of treatment was statistically significant (p-value = 0.0003). Subjects treated with IDELA + R also showed rapid and sustained improvements in the FACT-Leu Total and Trial Outcome Index scores compared to subjects treated with placebo + R. The main effect of treatment was statistically significant for the FACT-Leu Total score and Trial Outcome Index score, p-value = 0.0039 and p-value = 0.0023, respectively.

A total of 80 subjects (76.9%) in the IDELA + R treatment group showed MID improvement from baseline (ie, 5-point improvement) in the Additional Concerns (Leukemia) Subscale score compared to 66 subjects (66.7%) subjects in the placebo + R treatment group.

Karnofsky Performance Status Results: Median improvement from baseline was higher for subjects treated with IDELA +R versus subjects treated with placebo + R, 10.0 versus 0.0, respectively.

EQ-5D Questionnaire Results: Based on the Visual Analog Scale, subjects on IDELA + R showed improvement over baseline and consistently showed greater symptom improvement than subjects on placebo + R throughout the study.

Pharmacokinetics Results: In general, IDELA and GS-563117 plasma concentrations at predose or 1.5 hours postdose were comparable between Week 4 and Week 24. Mean trough concentrations of IDELA were comparable to those observed in other studies (eg, Study 101-02) and to the population PK modeling estimates derived using IDELA 150 mg twice daily monotherapy. Also, the mean IDELA concentrations were consistent with the lack of effect of rituximab coadministration on IDELA PK, as noted previously for covariate evaluation in the population PK analyses. In addition, plasma levels at trough were much greater than the EC_{50} for inhibition of PI3Kδ activity (39 nM).

Safety Results:

Final safety results of the study were consistent with the first and second interim analyses.

AEs: The most frequent AEs were consistent with those expected for a heavily pretreated, relapsed or refractory CLL population receiving immunochemotherapeutic agents. Fatigue was the most common event overall, occurring in 30.9% of subjects in the IDELA + R group and 33.3% of subjects in the placebo + R group. Grade 3 or higher fatigue occurred in 6 subjects (5.5%) in the IDELA + R group and 4 subjects (3.7%) in the placebo + R group. The most common AE in the IDELA + R group was pyrexia (IDELA + R: 40.0%; placebo + R: 18.5%). Grade 3 or higher pyrexia occurred in 2.7% of subjects in the IDELA + R group and 0.9% of subjects in the placebo + R group. When the incidences of the most common AEs were adjusted by total study drug exposure (accounting for the imbalance between treatment groups in time on study drug), the time-adjusted incidence of many AEs appeared to be generally balanced. A total of 15 AEs occurred more frequently in either treatment group with an associated p-value of relative risk ≤ 0.1. Two events had higher rates in the placebo + R group (early satiety and infusion-related reaction) and 13 events had higher rates in the IDELA + R group (pyrexia, GERD, ALT increased, AST increased, dehydration, rash, colitis, pain, diarrhea, chest discomfort, fall, sinus congestion, and stomatitis).

AEs of Interest: Thirty-two subjects (29.1%) in the IDELA + R group had an AE of diarrhea (any grade), and 10 subjects (9.1%) had events that were ≥ Grade 3 in severity (9 subjects with Grade 3 and 1 subject with Grade 4). In the placebo + R group, 19 subjects (17.6%) had diarrhea of any grade, and no subjects had diarrhea events that were ≥ Grade 3 in severity. Adverse events of colitis were reported for 8 subjects (7.3%) in the IDELA + R group and 1 subject (0.9%) in the placebo + R group. Five of the 8 subjects in the IDELA + R group with AEs of colitis also were reported to have AEs of diarrhea (3 of which were concurrent), and the 2 AE terms may have been used interchangeably for these subjects. Colitis AEs of Grade 3 in severity were reported for 5 subjects (4.5%) in the IDELA + R group; no subjects had Grade 4 colitis. No subject in the placebo + R group had ≥ Grade 3 colitis.

Sixteen subjects (14.5%) in the IDELA + R group had rash of any grade, and 1 subject (0.9%) had rash of ≥ Grade 3 in severity (there were no events that were Grade 4). In the placebo + R group, 5 subjects (4.6%) had rash, with no events of ≥ Grade 3 in severity. Maculo-papular rash was reported for 4 subjects (3.6%) in the IDELA + R group (1 event [0.9%] of Grade 3) and for no subjects in the placebo + R group. To further characterize the occurrence of rash in the IDELA development program, a review of all AE preferred terms potentially related to rash was conducted for the safety population. A search of MedDRA preferred terms (including the terms: dermatitis exfoliative, drug eruption, exfoliative rash, rash, rash erythematous, rash generalized,

rash macular, rash maculo-papular, rash morbiliform, rash papular, and rash pruritic was conducted). Twenty-seven subjects (24.5%) in the IDELA + R arm had an event within this medical search term (MST) rash classification, compared to 7 subjects (6.5%) in the placebo + R arm. This included 4 subjects (3.6%) in the IDELA + R arm with events that were Grade 3, compared to 1 subject (0.9%) in the placebo + R arm with events that were Grade 3 (there were no subjects in either arm with an event of Grade 4). In the IDELA +R group, 2 subjects (1.8%) discontinued due to one of the rash MST terms, compared to no subjects in the placebo + R group.

Six subjects (5.5%) in the IDELA + R group had pneumonitis of any grade, and 4 subjects (3.6%) had pneumonitis of ≥ Grade 3 in severity. In the placebo + R group, 1 subject (0.9%) had pneumonitis, and the event was of ≥ Grade 3 severity. There were no Grade 4 events of pneumonitis in either treatment group.

Deaths: Fifty-seven subjects died following at least 1 dose of study drug. A lower incidence of death was observed among subjects in the IDELA + R group (15.5%, 17 subjects) compared with the placebo + R group (37.0%, 40 subjects). Of the 57 subjects who died, 26 died on Study GS-US-312-0116 and 31 died on Study GS-US-312-0117. Causes of death were consistent with advanced CLL and the underlying frailty, age, and poor prognosis of the study population. TEAEs leading to the death of more than 1 subject in either treatment group were sepsis and pneumonia, each occurring in 2 subjects (1.9%) in the placebo + R group. Sepsis led to death in 1 subject in the IDELA + rituximab group, and pneumonia led to death in 0 subjects in the IDELA + rituximab group.

SAEs: SAEs were common in both treatment groups, reported for 49.5% of subjects overall (IDELA + R: 59.1%; placebo + R: 39.8%). Serious AEs were typical of the population, with infections and infestations, and blood and lymphatic system disorders accounting for most of the subjects with SAEs. Increased rates of pneumonitis and pyrexia were noted in the IDELA + R group compared with the placebo + R group.

Study Drug Discontinuations Due to AEs: Study drug discontinuations due to AEs were infrequent, occurring in 17.3% of subjects in the IDELA + R group and 12% of subjects in the placebo + R group. Six subjects in the IDELA + R group discontinued study drug due to AEs of diarrhea or colitis; the events resolved following study drug discontinuation in 5 of the 6 subjects. The sixth subject died of fungal pneumonia and febrile neutropenia before the diarrhea resolved. Two subjects (1.8%) in the IDELA + R treatment group discontinued the study for AEs related to transaminase elevation.

Clinical Laboratory Evaluations: As expected based on entry criteria, hematologic abnormalities were common among subjects in both treatment groups. Hemoglobin concentrations and platelet counts trended upward with time for both treatment groups.

Laboratory Evaluations of Interest: Based on results of prior studies with IDELA, elevations of ALT (all grades) occurred more commonly in the IDELA + R group (39.1%) than in the placebo + R group (12.0%). Most ALT elevations were mild or moderate; Grade 3 or 4 ALT elevations occurred in 10 subjects (9.1%) in the IDELA + R group and 1 subject (0.9%) in the placebo + R group. Elevations of AST (all grades) also occurred more commonly in the IDELA + R group (28.2%) than in the placebo + R group (14.8%). Grade 3 or 4 AST elevations occurred in 6 subjects (5.5%) in the IDELA + R group and no subjects in the placebo + R group.

Seven subjects in the IDELA + R group had Grade ≥ 3 transaminase elevations that led to interruption of study drug. All 7 subjects had Grade ≥ 3 elevations in ALT with concurrent AST elevations that ranged from Grade 1 to Grade 4. Study drug was reinitiated at 100 or 150 mg in these 7 subjects. Following reinitiation, 4 of these subjects had additional Grade 3 or 4 transaminase elevations, commencing between 7 and 125 days following resolution of the first. One subject in the placebo + R group also had study drug withholding for transaminase elevations (Grade 3 ALT; Grade 1 AST); this subject was successfully rechallenged when the event resolved. Two subjects (1.8%) in the IDELA + R treatment group and no subjects in the placebo + R treatment group discontinued the study for AEs related to transaminase elevation.

Seventy-one subjects (64.5%) in the IDELA + R group were reported to have decreased neutrophil count of any grade, and 26 subjects (23.6%) had decreased neutrophil count of Grade 3 in severity, while 20 (18.2%) had a decrease of Grade 4 in severity. In the placebo + R group, 61 subjects (56.5%) had decreased neutrophil count of any grade: 19 subjects (17.6%) had decreases of Grade 3 in severity and 14 subjects (13.0%) had decreases of Grade 4 in severity. Median ANC levels over time remained stable in both treatment groups.

CONCLUSIONS

The overall conclusions from this final analysis of Study GS-US-312-0116 are consistent with those reached from the first and second interim analyses, and are as follows:

- In this study population of subjects with relapsed or refractory, heavily pretreated, poor prognosis CLL who were older and had significant comorbidities, PFS, the primary efficacy endpoint, was statistically significantly and overwhelmingly in favor of IDELA + R compared with placebo + R, with an adjusted hazard ratio of 0.15 and a 2-sided p-value of 1.6×10^{-16}.
- PFS results favored IDELA + R compared with placebo + R across all predefined subgroups. Most importantly, the treatment effect was the same in the subgroups with the most adverse cytogenetics, 17p deletion and *TP53* mutation or unmutated *IGHV*, indicating that IDELA is remarkably effective regardless of CLL genetic status.
- Analyses strongly favored IDELA + R over placebo + R for ORR (IDELA + R: 83.6%, placebo + R: 15.5%; odds ratio 27.76; p-value = 1.3×10^{-23}) based on the ITT Analysis Set.
- LNR rate results favored IDELA + R over placebo + R; stratified odds ratio (95% CI) was 225.83; p-value = 8.5×10^{-38}. LNR rate results favored IDELA + R over placebo + R across all predefined subgroups.
- The primary OS analysis was performed using the ITT Analysis Set (according to the original randomization) which included all available survival information from Study GS-US-312-0116 (including long-term follow-up data) and its companion Study GS-US-312-0117 (including long-term follow-up data up to the cutoff date of 01 July 2014). A total of 57 subjects died (IDELA + R: 17 subjects; 15.5%; placebo + R: 40 subjects, 36.4%). IDELA + R demonstrated a statistically significant improvement in OS. The adjusted hazard ratio (95% CI) for OS was 0.34 (0.19, 0.60), with a p-value from stratified log-rank test of 0.0001. The adjusted hazard ratio (95% CI) for the OS sensitivity analysis that included data from GS-US-312-0117 was 0.43 (0.20, 0.95) with a p-value from stratified log-rank test = 0.0332.

- For the Additional Concerns (Leukemia-subscale), FACT-Leu Total, and the Trial Outcome Index scores of the HRQL FACT-Leu Questionnaire, subjects treated with IDELA + R consistently showed greater symptom improvement than subjects on placebo + R at each timepoint throughout the study. Subjects treated with IDELA + R reached the MID for Additional Concerns rapidly (Week 4) and their improvement was sustained, whereas subjects on placebo + R reached MID at Week 72. In the mixed-effects model analysis of the changes from baseline in the Additional Concerns, FACT-Leu Total and Trial Outcome Index scores, the main effect of treatment was statistically significant with p-values of 0.0003, 0.0039, and 0.0023, respectively.
- IDELA was generally well tolerated and had a manageable safety profile in combination with rituximab. Most AEs were consistent with those expected for a heavily pretreated, relapsed/refractory CLL population. The most frequently reported AE overall was fatigue, occurring in 30.9% of subjects in the IDELA + R group and 33.3% of subjects in the placebo + R group. The most common AE in the IDELA + R group was pyrexia (IDELA + R: 40.0%; placebo + R: 18.5%). Diarrhea, vomiting, chills, and rash also occurred in the IDELA + R group at a higher incidence than with placebo + R. AEs that occurred more frequently in the IDELA + R group with an associated p-value of relative risk ≤ 0.1 were pyrexia, GERD, ALT increased, AST increased, dehydration, rash, colitis, pain, diarrhea, chest discomfort, fall, sinus congestion, and stomatitis. The results of this final analysis are consistent with the safety profile of IDELA.
- As previously observed in studies of IDELA monotherapy, early transaminase elevations occurred that were generally asymptomatic and transient. Transaminase elevations led to interruption of study drug in 7 subjects in the IDELA + R group; study drug was reinitiated in these subjects with 4 subjects experiencing additional Grade 3 or 4 transaminase elevations. Two subjects (1.8%) in the IDELA + R treatment group and no subject in the placebo + R treatment group discontinued the study for AEs related to transaminase elevation.
- The efficacy and safety findings in this study strongly support a positive benefit-risk evaluation for the use of IDELA, an oral PI3Kδ pathway inhibitor, in combination with rituximab in this population of elderly subjects with poor prognosis and limited or no treatment options.