INTERIM 1 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 Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (Zydelig®, GS-1101)
Dose and Formulation:	150-mg tablet taken orally twice daily
Indication:	Chronic Lymphocytic Leukemia
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-312-0115
Phase of Development:	Phase 3
IND No.:	101254
EudraCT No.:	2011-006292-20
ClinicalTrials.gov Identifier:	NCT01569295
Study Start Date:	15 June 2012 (First Subject Screened)
Study End Date:	07 October 2015 (Last Subject Observation for the Primary Analysis) 02 May 2016 (Last Subject Observation for Follow-Up Assessments of Safety and Overall Survival)
Principal or Coordinating Investigator:	Name: Andrew D. Zelenetz, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Henry Adewoye, MD Telephone: PPD Fax: PPD
Report Date:	16 November 2016

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-312-0115
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
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 Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Investigators: Multicenter study

Study Centers: Subjects were enrolled at total of 110 sites in the following countries: Australia, Belgium, Canada, Croatia, Czech Republic, France, Greece, Hungary, Ireland, Italy, New Zealand, Poland, Portugal, Romania, Russia, Spain, Turkey, United Kingdom, and United States.

Publications: Zelenetz AD, Robak T, et al. Idelalisib Plus Bendamustine and Rituximab (BR) Is Superior to BR Alone in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study. American Society of Hematology (ASH) 57th Annual Meeting & Exposition; 5-8 December 2015; Orlando, FL.

Barrientos JC, Brown JR, et al. Results of a Randomized Double-Blind Placebo-Controlled Phase 3 study Evaluating Idelalisib in Combination with Bendamustine and Rituximab in Patients with Relapsed/Refractory CLL and Adverse Prognostic Features. American Society of Clinical Oncology (ASCO) 2016 Annual Meeting; 3-7 June 2016; Chicago, IL.

Hillmen, P, Ferra C, et al. Idelalisib in Combination with Bendamustine and Rituximab Improves Overall Survival in Patients with Relapsed/Refractory CLL: Interim Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study. European Hematology Association (EHA) 21st Annual Meeting; 9-12 June 2016; Copenhagen, Denmark.

Study Period:

15 June 2012 (First Subject Screened)
07 October 2015 (Last Subject Observation for the Primary Analysis)
02 May 2016 (Last Subject Observation for Follow-Up Assessments of Safety and Overall Survival [OS])

Phase of Development: Phase 3

Objective

The primary objective of this study was as follows:

- To evaluate the effect of the addition of idelalisib (IDL [GS-1101, Zydelig®]) to bendamustine + rituximab (BR) on progression-free survival (PFS) in subjects with previously treated chronic lymphocytic leukemia (CLL)

The secondary objective of this study was as follows:

- To evaluate the effect of the addition of IDL to BR on the onset, magnitude, and duration of tumor control

The tertiary objectives of this study were as follows:

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

Methodology: Study GS-US-312-0115 is a Phase 3, global randomized, double-blind, placebo-controlled study.

Subjects were stratified based on 17p deletion and/or TP53 mutation in CLL cells (either versus neither [or indeterminate]), immunoglobulin heavy chain variable region (IGHV) mutation (unmutated [or IGHV3-21] versus mutated [or indeterminate]), and disease status (refractory [CLL progression < 6 months from completion of prior therapy] versus relapsed [CLL progression ≥ 6 months from completion of prior therapy]) and randomized in a 1:1 ratio to receive 1 of the 2 treatments.

All subjects received rituximab with a planned dosing regimen of 375 mg/m^2 intravenously on Day 1 in the first cycle and 500 mg/m^2 intravenously on Day 1 of each of the subsequent 5 cycles (6 cycles total; 4 weeks per cycle). Bendamustine was administered intravenously at a starting dose of 70 mg/m^2/infusion; bendamustine was given on Days 1 and 2 of each of the 6 planned cycles. Bendamustine and rituximab were administered until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable bendamustine- or rituximab-related toxicity, pregnancy, substantial noncompliance with study procedures, study discontinuation, or a maximum of 6 cycles.

Idelalisib 150 mg taken orally (PO) twice daily (BID) or matching placebo PO BID was administered continuously until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation, even if bendamustine and/or rituximab were discontinued.

Clinic/laboratory visits occurred every 2 weeks through Week 24 and every 6 weeks between Weeks 24 and 48. Subjects who continued on study treatment past Week 48 had clinic visits every 12 weeks. Subjects were assessed for safety at each clinic visit. Subjects were assessed for CLL disease status by physical and laboratory examinations at each clinic visit and by computed tomography (CT) or magnetic resonance imaging (MRI) at Weeks 12, 24, 36, and 48 and every 12 weeks thereafter until definitive progression.

Number of Subjects (Planned and Analyzed):
Planned: 390 subjects
Analyzed: 416 subjects
(207 subjects received IDL + BR and 209 subjects received placebo + BR)

Diagnosis and Main Criteria for Inclusion: The target population consisted of adult subjects with previously treated CLL who had measurable lymphadenopathy, required therapy for CLL, had received prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody, CLL that was not refractory to bendamustine, had experienced CLL progression < 36 months since the completion of the last prior therapy, and were sufficiently fit to receive cytotoxic therapy. Key inclusion criteria were as follows:

- Diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records
- CLL that warrants treatment (consistent with accepted IWCLL criteria for initiation of therapy)
- Presence of measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by CT or MRI)
- Prior treatment for CLL comprising:
  1) ≥ 2 cycles of a regimen containing a purine analog (eg, fludarabine, pentostatin, cladribine) or bendamustine, and
  2) ≥ 2 doses with a regimen containing an anti-CD20 monoclonal antibody (eg, rituximab, ofatumumab, obinutuzumab)
- Documentation of CLL progression < 36 months since the completion of the last prior therapy for CLL
- Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥ 3 weeks before randomization
- 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 or 2 permitted])
- Karnofsky performance status (KPS) score of ≥ 60

Duration of Treatment:
IDL/placebo was taken continuously.
Rituximab and bendamustine were administered up to a maximum of 6 and 12 infusions, respectively.

Test Product, Dose, and Mode of Administration:
IDL: 150 mg/dose taken orally twice daily starting on Day 1 and administered continuously thereafter.
Lot numbers administered in this study to date:

IDL 150 mg: CV1104D3, CV1107D1, CY1202B1, CV1204B1, CV1302D1, CV1303B1, CV1401B1

IDL 100 mg: CV1104C1, CV1107B2, CY1201B1, CV1304C1, CV1404D1

Placebo 150 mg: CV1108D1, CV1203B1

Placebo 100 mg: CV1108C1, CV1109B1

Reference Therapy, Dose, Mode of Administration, and Lot No.:
Rituximab: 375 mg/m^2 intravenously on Day 1 of the first 28-day cycle of treatment; followed by 500 mg/m^2 intravenously on Day 1 of each of 5 subsequent 28-day cycles of treatment up to 6 total cycles (6 infusions) as tolerated

Lot numbers administered in this study to date: H0560B03, H0603B01

Bendamustine: 70 mg/m^2/dose intravenously on Day 1 and Day 2 of each 28-day cycle of treatment up to 6 total cycles (12 infusions) as tolerated

Lot numbers administered in this study to date: 102979, 102382

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

- PFS – defined as the interval from randomization to the earlier of 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 for which sequential testing was performed to control Type 1 error rate. Secondary endpoints were overall response rate (ORR), lymph node response (LNR) rate, OS, and complete response (CR) rate.

Tumor Control

- ORR – defined as the proportion of subjects who achieved a CR, complete response with incomplete marrow recovery (CRi,) or partial response (PR)
- LNR rate – defined as the proportion of subjects who achieved a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions
- CR rate – defined as the proportion of subjects who achieved a CR
- Time to response (TTR) – defined as the interval from randomization to the first documentation of confirmed CR, CRi, or PR

- Duration of response (DOR) – defined as the interval from the first documentation of confirmed CR, CRi, 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 from baseline (minimum decrease of 2 cm) in the enlargement of the spleen in its longest vertical dimension (LVD) or to ≤ 12 cm by imaging
- Hepatomegaly response rate – defined as the proportion of subjects with a 50% decrease from baseline in the enlargement of the liver in its LVD or ≤ 18 cm by imaging
- Absolute lymphocyte count (ALC) response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC ≥ 4×10^9/L) who achieved an on-study ALC < 4×10^9/L or demonstrated a ≥ 50% decrease in ALC from baseline. ALC values within 4 weeks postbaseline were excluded from the ALC response rate evaluation.
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count < 100×10^9/L) who achieved an on-study platelet count ≥ 100×10^9/L or demonstrated a ≥ 50% increase in platelet count from baseline without need for supportive care (eg, transfusion or growth factor). Platelet values within 4 weeks postbaseline 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 achieved an on-study hemoglobin ≥ 110 g/L (11.0 g/dL) or demonstrated a ≥ 50% increase in hemoglobin from baseline without supportive care (eg, red blood cell transfusions or growth factor). Hemoglobin values within 4 weeks postbaseline were excluded from the hemoglobin response rate evaluation.
- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] ≤ 1.5×10^9/L) who achieved an ANC > 1.5×10^9/L or demonstrated a ≥ 50% increase in ANC from baseline without need for exogenous growth factors. ANC values within 4 weeks postbaseline were excluded from the neutrophil response rate evaluation.

Patient Well-Being

- OS – defined as the interval from randomization to death from any cause
- Change from baseline in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) questionnaire
- Changes from baseline in KPS

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) IDL 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(s)

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

Statistical Methods:

An independent review committee (IRC) reviewed blinded radiographic data and pertinent clinical data in order to provide expert evaluation of disease status. The findings of the IRC were considered primary for analyses of PFS and other tumor-control endpoints.

One formal interim analysis was planned for this study after reaching approximately 66% of total PFS events (definitive CLL progression or death). Based on results from this prespecified analysis (data cutoff date of 15 June 2015, by which time 75% of PFS events had occurred), the independent data monitoring committee (DMC) recommended stopping the study for efficacy. Upon review of the data and in discussion with regulatory agencies, Gilead made the decision to stop the study early. Treatment assignments were unblinded on 16 November 2015; at that time, 81 subjects were receiving IDL + BR and 34 subjects were receiving placebo + BR. Subjects randomized to placebo discontinued treatment and continued with the study procedures per protocol.

The efficacy data presented in this interim clinical study report reflect a data cutoff date of 07 October 2015. The safety data and follow-up data for OS reflect a data cutoff date of 02 May 2016 in order to provide the longest possible follow-up information.

Statistical Analysis of the Primary Endpoint:

The primary endpoint for this study was PFS. The date of definitive CLL progression was the time point at which progression was identified by relevant objective radiographic and/or clinical data per IRC. Data were censored on the date of the last tumor assessment (including assessments with an outcome of not evaluable) for subjects who did not have disease progression or subjects who had not died prior to the end of study. Data were censored on the date of the last tumor assessment prior to the initiation of new antitumor therapy (including assessments with an outcome of not evaluable) for subjects who started new antitumor therapy prior to documented disease progression. Data were censored on the date of the last tumor assessment prior to ≥ 2 consecutive missing tumor assessments (including assessments with an outcome of not evaluable) for subjects who had ≥ 2 consecutive missing tumor assessments before disease progression or death. Subjects without adequate baseline tumor response evaluation were censored on the randomization date.

The statistical hypothesis for the primary endpoint of PFS was as follows: H_0: hazard ratio (HR) for PFS equals 1 between Group A (IDL + BR) and Group B (placebo + BR) versus H_1: HR for PFS is less than 1 (Group A is superior to Group B in terms of PFS). PFS between the 2 treatment groups was compared, based on the intent-to-treat (ITT) Analysis Set using a stratified log-rank test, adjusted for stratification factors. Medians, first quartile (Q1),

third quartile (Q3), the proportion of subjects who were progression free at 6 months and 12 months from randomization (based on Kaplan-Meier [KM] estimates), HR, and corresponding 95% confidence interval (CI; as calculated using a Cox proportional hazards regression model) were presented. A Kaplan-Meier curve was 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 KM method and the stratified log-rank test, and 3) analysis of PFS in which surviving, nonprogressing subjects who were lost to follow-up were categorized as having an event at the time of the last known CLL tumor status assessment if they were in Group A, and were categorized as censored at the time of the last known CLL tumor status assessment if they were in Group B.

Statistical Analysis of the Secondary Endpoints:

Secondary efficacy endpoints were ORR, LNR rate, OS, and CR rate.

To preserve the overall type I error rate across the primary and secondary endpoints of the study at a 2-sided significance level of 0.05, the primary endpoint analysis served as a gatekeeper for the secondary endpoint analyses; ie, the primary hypothesis relating to PFS (the null hypothesis) was to be rejected at the prespecified significance level before the efficacy hypotheses for the secondary efficacy endpoints were to be evaluated. If the primary hypothesis was rejected, the 4 secondary endpoints were to be tested sequentially at the 2-sided significance level of 0.032 in the order listed (ORR, LNR rate, OS, and CR rate). If a null hypothesis in the sequence described above was not rejected, formal sequential testing was to be stopped, and only nominal significance was to be cited for the remaining secondary endpoints.

Differences in number and percentage of subjects experiencing ORR (CR, CRi, or PR during the study and maintained for at least 12 weeks with a 1-week window) were compared between treatment groups using Cochran-Mantel-Haenszel Chi-square tests after adjusting for stratification factors. Odds ratios and the corresponding 95% CIs were presented as well. The potential influence of subject baseline characteristics (gender, age, race, number of prior therapies, disease staging, etc.) and of treatment on response rates were explored with logistic regression modeling.

Differences in the LNR rate between the 2 treatment groups were compared using Cochran-Mantel Haenszel (CMH) Chi-square tests after adjusting for stratification factors. Only subjects who had both baseline and at least 1 evaluable postbaseline SPD were included in this analysis.

The OS analysis was performed using the ITT Analysis Set (according to the original randomization) and included all available survival information during the study with long-term follow-up to the data cutoff date of 07 October 2015 for the initial assessment and to the data cutoff date of 02 May 2016 for the follow-up assessment. Data from surviving subjects were censored at the last time that the subject was known to be alive on study or in long-term follow-up. Differences between the treatment groups in OS were assessed using a stratified log-rank test, adjusted for stratification factors. Median, Q1, Q3, HR, and corresponding 95% CI were presented by treatment group. Plots of time to event by treatment group were provided using the KM method.

Differences in the CR rate between the 2 treatment groups were compared using Fisher's exact test due to the small number of CRs.

Exploratory Endpoints:

Exploratory endpoints included TTR, DOR, percentage change in lymph node area (assessed using SPD), splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate, neutrophil response rate, changes in HRQL as reported by subjects using the FACT-Leu questionnaire, changes in performance status as documented using the Karnofsky performance criteria, and changes in overall health and single-item dimension scores as assessed using the EQ-5D questionnaire.

Time to response and DOR were evaluated using IRC assessments based on the subset of ITT subjects who achieved a CR, CRi, or PR and maintained the response for at least 12 weeks (± 1 week). Descriptive statistics were provided for TTR. DOR was summarized using KM methods (median, Q1, Q3, and corresponding 95% CI) and a plot of the KM curve for DOR was provided by treatment group.

The best percent change in SPD from baseline during the study was summarized using descriptive statistics. Only SPDs prior to receiving other anti-tumor therapy were included. The best percent change from baseline in SPD was defined as the largest decrease in tumor size during the study. Waterfall plots of best on-study percent change in SPD were provided for each treatment group using IRC data.

Splenomegaly, hepatomegaly, ALC, platelet, hemoglobin, and neutrophil response rates were presented with 95% CIs.

The HRQL analyses were based on the ITT Analysis Set. The mean and change from baseline in mean scores to each subsequent assessment were summarized for subscale and composite scores. The best change from baseline during the study, defined as the highest positive value among all postbaseline visits minus the baseline value, was also summarized. Changes from baseline in FACT-Leu subscales and composite scores were analyzed using mixed-effects models by including treatment, time, treatment-by-time interaction, and stratification factors as fixed effects. The least squares means of change from baseline over time was plotted. Subjects with minimally important differences (MID) in the subscales were analyzed by KM method, and the proportion of subjects with any improvement was summarized.

The KPS scores and the change from baseline scores to each subsequent assessment were summarized. The best changes from baseline during the study were also summarized.

The frequency and proportion of reported problems for each level of every EQ-5D dimension were summarized at each assessment time point. EQ-5D was converted into a single utility index by applying United States (US) preference-weighted index. The mean and change from baseline in mean EQ visual analogue scale (EQ VAS) scores and EQ-5D utility index to each subsequent assessment were summarized. The best change from baseline during the study, defined as the highest positive value among all postbaseline visits minus the baseline value, was also summarized.

Exposure:

Idelalisib plasma concentrations immediately predose and at 1.5 hours after IDL dose administration at various clinic visits were summarized by treatment and visit using descriptive statistics. A separate biomarker analysis plan will be prepared to detail pharmacodynamics and biomarker analyses.

Safety:

All AEs were listed. The focus of AE summarization was on treatment-emergent AEs (TEAEs). A TEAE was defined as an event that met 1 of the following criteria: (1) an adverse event with onset date on or after the start of treatment and up to 30 days after the permanent discontinuation of study treatment, (2) an adverse event resulting in treatment discontinuation after the start of treatment.

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. The severity of AEs was graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, whenever possible.

Summaries (number and percentage of subjects) of TEAEs (by system organ class [SOC] and preferred term [PT]) were provided by treatment groups for the following: AEs; AEs by CTCAE grade; ≥ Grade 3 AEs; IDL/placebo, rituximab and bendamustine-related AEs ; SAEs; IDL/placebo, rituximab, and bendamustine-related SAEs; AEs leading to IDL/placebo interruption, AEs leading to IDL/placebo reduction; AEs leading to IDL/placebo, rituximab and bendamustine discontinuation; AEs leading to death; AEs of interest (AEIs) by 12-week time intervals, and AE incidence rate adjusted for total exposure.

Summaries of baseline and worst postbaseline treatment-emergent laboratory abnormalities were provided by treatment groups. Exposure-adjusted treatment-emergent lab abnormalities were analyzed.

SUMMARY OF RESULTS:

The efficacy data presented in this interim clinical study report reflect a data cutoff date of 07 October 2015. The safety data and follow-up data for OS reflect a data cutoff date of 02 May 2016.

Subject Disposition, Demographics, and Baseline and Disease Characteristics:

At the time of the primary analysis (data cutoff date of 07 October 2015), 43.5% (90 subjects) in the IDL + BR group were continuing treatment, 16.4% (34 subjects) were not continuing treatment due to the investigator assessing the subject as meeting the primary endpoint, and 40.1% (83 subjects) had discontinued treatment for other reasons. In the placebo + BR group, 21.5% (45 subjects) were continuing treatment, 47.8% (100 subjects) were not continuing treatment due to the investigator assessing the subject as meeting the primary endpoint and 30.6% (64 subjects) had discontinued treatment for other reasons. Investigators cited AEs as the reason for discontinuation from treatment in 27.1% (56 subjects) in the IDL + BR group and 13.4% (28 subjects) in the placebo + BR group.

Through the database cutoff date for this report (02 May 2016), 31.4% (65 subjects) in the IDL + BR group were continuing treatment, 20.3% (42 subjects) were not continuing treatment due to the investigator assessing the subject as meeting the primary endpoint, and 48.3% (100 subjects) had discontinued treatment for other reasons. In the placebo + BR group, 0.5% (1 subject) were continuing treatment, 55.0% (115 subjects) were not continuing treatment due to the investigator assessing the subject as meeting the primary endpoint, and 44.0% (92 subjects) had discontinued treatment for other reasons. Note, for 1 subject in the placebo + BR group (Subject PPD treatment was listed as ongoing in this summary due to a data entry error; no subject in the placebo + BR group was continuing treatment at the data cutoff date of 02 May 2016. Investigators cited AEs as the reason for discontinuation from treatment in 30.9% (64 subjects) in the IDL + BR group and 13.9% (29 subjects) in the placebo + BR group.

At the time of the primary analysis (data cutoff date of 07 October 2015), 33.9% (141 subjects) of the total study population were ongoing in the study: 45.9% (95 subjects) in the IDL + BR group and 22.0% (46 subjects) in the placebo + BR group. Investigators assessed that the primary study endpoint of PD or death had been met by 28.0% (58 subjects) in the IDL + BR group and 57.4% (120 subjects) in the placebo + BR group. In the IDL + BR and placebo + BR groups, 26.1% (54 subjects) and 20.6% (43 subjects), respectively, discontinued the study for other reasons. In the IDL + BR group, the primary reason for discontinuation was AEs (12.1% [25 subjects]) followed by withdrawal by subject (7.2% [15 subjects]). In the placebo + BR group, the primary reason for discontinuation was physician's decision (8.6% [18 subjects]) followed by AEs (6.7% [14 subjects]).

Through the database cutoff date for this report (02 May 2016), 22.4% (93 subjects) of the total study population were ongoing in the study: 33.8% (70 subjects) in the IDL + BR group and 11.0% (23 subjects) in the placebo + BR group. Investigators assessed that the primary study endpoint of PD or death had been met by 35.3% (73 subjects) in the IDL + BR group and 67.9% (142 subjects) in the placebo + BR group. In the IDL + BR and placebo + BR groups, 30.9% (64 subjects) and 21.1% (44 subjects), respectively, discontinued the study for other reasons. In the IDL + BR group, the primary reason for discontinuation was AEs (13.0% [27 subjects]) followed by withdrawal by subject (9.7% [20 subjects]). In the placebo + BR group, the primary reason for discontinuation was physician's decision (9.1% [19 subjects]) followed by AEs (6.2% [13 subjects]).

Overall, demographics and baseline characteristics (age, sex, race, BMI) were comparable between the 2 treatment groups. The median (Q1, Q3) age was 63 (56, 70) years with an age range of 32 to 83 years. A total of 175 subjects (42.1%) were ≥ 65 years of age. The majority of subjects were male (76.0%), white (90.6%), and identified as not Hispanic or Latino (91.3%). The median (Q1, Q3) baseline BMI was 27.3 (24.5, 30.6) kg/m^2. Most subjects (331 subjects; 79.6%) had a reduced KPS (ie, KPS score 50 to 90) at study entry, 67.1% had modest reduction (ie, KPS score 80 to 90), and 12.3% had significant reduction (ie, KPS score 60 to 70).

Prior to study entry, the subject population had presented with CLL for a median (Q1, Q3) of 6.2 (3.9, 9.4) years with a range of 0.1 to 23.4 years. At study screening, 47.8% versus 41.6% of subjects had Rai disease stages III/IV in the IDL + BR group versus placebo + BR group, respectively. Other disease characteristics were balanced between treatment groups. Approximately 33% of the population had 17p deletion and/or TP53 mutation, approximately 83% of the population had unmutated IGHV, and approximately 33% of the population had refractory disease.

Treatment groups were balanced with respect to the incidence and type of prior CLL regimens. The median (Q1, Q3) number of prior CLL regimens was 2.0 (1.0, 4.0) with a range of 1 to 13 prior regimens received. The most common prior regimens were fludarabine + cyclophosphamide + rituximab (66.8%; 278 subjects), fludarabine + cyclophosphamide (22.4%; 93 subjects), single-agent chlorambucil (18.0%; 75 subjects), and bendamustine + rituximab (11.3%, 47 subjects). The median (Q1, Q3) time since last prior regimen was 18.1 (4.8, 26.9) months for subjects in the IDL + BR group and 13.9 (5.9, 27.2) months for subjects in the placebo + BR group.

Efficacy Results:

Primary Endpoint:

Primary efficacy results are based on data through 07 October 2015.

Progression-Free Survival: An analysis of PFS, as assessed by the IRC and based on the ITT Analysis Set, showed that IDL + BR was superior to placebo + BR. A total of 40.6% (84 subjects) of the IDL + BR group and 71.3% (149 subjects) of the placebo + BR group reported a PFS event, with an adjusted HR (95% CI) of 0.33 (0.25, 0.44) and 2-sided p-value of < 0.0001 based on a stratified log-rank test. The median (95% CI) PFS was 20.8 (16.6, 26.4) months for subjects in the IDL + BR group and 11.1 (8.9, 11.1) months for subjects in the placebo + BR group. Progression-free survival following treatment with IDL + BR was improved compared to treatment with placebo + BR in all prespecified subgroups, including subjects with 17p deletion and/or TP53 mutation, subjects with mutated or unmutated IGHV, relapsed and refractory subjects, males, females, subjects < 65 years, subjects ≥ 65 years, whites, and nonwhites.

Secondary Endpoints:

Secondary efficacy results are based on data through 07 October 2015, with follow-up OS results based on data through 02 May 2016.

ORR: Based on the ITT Analysis Set, the ORR (classified as CR, CRi, or PR with minimal duration of 12 weeks) (95% CI) was 70.0% (63.3, 76.2) for the IDL + BR group and 45.0% (38.1, 52.0) for the placebo + BR group. The odds ratio (95% CI) for the ORR was 3.09 (2.02, 4.72), which favored IDL + BR compared with placebo + BR (p-value < 0.0001).

LNR rate: Based on the ITT Analysis Set, the LNR rate (95% CI) was 96.9% (93.3, 98.8) for the IDL + BR group and 60.9% (53.7, 67.8) for the placebo + BR group, respectively. The stratified odds ratio (95% CI) for the LNR rate was 28.72 (10.48, 78.72), which favored IDL + BR compared with placebo + BR (p-value < 0.0001).

OS: The primary OS analysis was performed using the ITT Analysis Set. Based on data through 07 October 2015, a total of 102 subjects had died on study, 43 subjects (20.8%) in the IDL + BR group and 59 subjects (28.2%) in the placebo + BR group. The adjusted HR (95% CI) for OS was 0.62 (0.42, 0.92), which favored IDL + BR compared with placebo + BR (p-value from stratified log-rank test = 0.0309). OS results favoring IDL + BR over placebo + BR were demonstrated across all prespecified subgroups.

A follow-up OS analysis was performed using data through 02 May 2016. Between 07 October 2015 and 02 May 2016, an additional 21 subject deaths were reported, 10 in the IDL + BR group and 11 in the placebo + BR group. As of 02 May 2016, a total of 123 subjects had died, 53 subjects (25.6%) in the IDL + BR group and 70 subjects (33.5%) in the placebo + BR group. The adjusted HR (95% CI) for OS was 0.67 (0.47, 0.96), which favored IDL + BR compared with placebo + BR (p-value from stratified log-rank test = 0.0364). Consistent with OS results through 07 October 2015, OS results favoring IDL + BR over placebo + BR were demonstrated across all prespecified subgroups.

CR Rate: Of the 3 documented CRs on study, all occurred in the IDL + BR group (rate of 1.4%).

Exploratory Endpoints:

All exploratory efficacy results are based on data through 07 October 2015.

TTR: Among subjects who responded, the median (Q1, Q3) TTR was 2.9 (2.8, 3.3) months for both treatment groups (IDL + BR, N = 145; placebo + BR, N = 94).

DOR: The median (95% CI) DOR was 2-fold longer for subjects treated with IDL + BR (22.8 months [19.1, 27.2], N = 145) than for subjects treated with placebo + BR (11.2 months [8.5, 13.7], N = 94).

Best Percent Change in SPD: The best percent change in SPD was assessed among the subjects with measurable index lesions at baseline and at least 1 postbaseline visit. The median (Q1, Q3) best percent change in SPD was –82.6 (−89.0, −73.7) for subjects treated with IDL + BR and −59.8 (−76.8, −34.0) for subjects treated with placebo + BR.

Splenomegaly and Hepatomegaly Response Rates: The splenomegaly response rate (95% CI) was 84.5% (77.6, 89.9) in the IDL + BR group and 56.7% (48.1, 65.0) in the placebo + BR group. The hepatomegaly response rate (95% CI) was 57.6% (47.2, 67.5) in the IDL + BR group and 43.1% (33.7, 53.0) in the placebo + BR group.

Additional Response Rates: The ALC and ANC response rates were 99.4% and 85.7%, respectively, in the IDL + BR group and 95.8% and 81.3%, respectively, in the placebo + BR group. Platelet response and hemoglobin response rates were 88.8% and 87.9%, respectively, in the IDL + BR group and 77.8% and 70.4%, respectively, in the placebo + BR group.

HRQL: FACT-Leu Questionnaire Results: The median change from baseline in the Leukemia-Specific Subscale (Additional Concerns) scores reached the MID at Week 8 for the IDL + BR group and Week 16 for the placebo + BR group. Median changes observed for the IDL + BR group showed greater symptom improvement than those in the placebo + BR group at most timepoints throughout the first 48 weeks of the study, although the differences did not achieve statistical significance.

KPS Results: Median improvement from baseline was 10 points in the IDL + BR group and 0 points in the placebo + BR group.

EQ-5D Questionnaire Results: As assessed by the EQ VAS, health outcomes were maintained in both treatment groups with a more positive trend observed in the IDL + BR group. A statistically significant difference was observed at Week 36.

Pharmacokinetics Results: In general, IDL and its major metabolite, GS-563117, plasma concentrations were comparable at predose or 1.5 hours postdose between Week 4 and Week 24. Plasma concentrations of IDL were comparable to those observed in other studies (eg, Studies 101-02, GS-US-312-0116, and GS-US-312-0119) and to population PK modeling estimates following IDL 150 mg twice daily monotherapy. The results are consistent with the lack of effect of BR coadministration on IDL PK.

Safety Results: All safety results are based on data through 02 May 2016.

In the Safety Analysis Set, the median (Q1, Q3) duration of exposure to IDL in the IDL + BR group was 18.2 (5.8, 24.0) months, with a range of 0 to 43.4 months. The median (Q1, Q3) duration of exposure to placebo was 11.1 (5.8, 16.6) months in the placebo + BR group.

Subjects in both treatment groups had similar exposures to bendamustine and rituximab. The median (Q1, Q3) duration of exposure to bendamustine was 4.7 (3.0, 5.1) months in the IDL + BR group and 4.7 (3.1, 4.9) months in the placebo + BR group. The median (Q1, Q3) duration of exposure to rituximab was 4.7 (3.7, 5.2) months in the IDL + BR group and 4.6 (4.4, 4.9) months in the placebo + BR group.

Key safety findings are as follows:

AEs: Adverse events were common in both treatment groups, occurring in 100% (207 subjects) of the IDL + BR group and 97.1% (203 subjects) of the placebo + BR group. The most commonly reported AEs by treatment group were as follows:

- IDL + BR: neutropenia (63.8%, 132 subjects), pyrexia (43.5%, 90 subjects), and diarrhea (40.6%, 84 subjects)
- Placebo + BR: neutropenia (54.5%, 114 subjects), nausea (34.9%, 73 subjects), and pyrexia (30.1%, 63 subjects)

The AEs (any grade) with the highest adjusted incidence rates by treatment group were as follows:

- IDL + BR: neutropenia (1.12 events/subject-year), pyrexia (0.47 events/subject-year), and diarrhea (0.42 events/subject-year)
- Placebo + BR: neutropenia (0.96 events/subject-year), nausea (0.50 events/subject-year), and pyrexia (0.36 events/subject-year)

Subjects in the placebo + BR group had an adjusted incidence rate of 0.26 events/subject-year for diarrhea and subjects in the IDL + BR group had an adjusted incidence rate of 0.27 events/subject-year for nausea.

AEIs: AEs of interest for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade progressive multifocal leukoencephalopathy (PML), any grade pneumonitis, and ≥ Grade 3 rash by medical search terms (MST). No subject experienced a PML event during this study. Following from the safety findings identified in March 2016, AEIs of infection (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade cytomegalovirus [CMV] infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]) were added.

One subject (0.5%) in the IDL + BR group and no subject in the placebo + BR group had an AE of diverticular perforation. This subject reported a Grade 4 SAE of diverticular perforation with time to onset of 28.3 weeks and resolution on the same day. The SAE was assessed by the investigator as unrelated to IDL or BR.

A total of 28 subjects (13.5%) in the IDL + BR group and 4 subjects (1.9%) in the placebo + BR group had ≥ Grade 3 diarrhea and/or colitis. The exposure-adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.10 events/subject-year in the IDL + BR group compared with 0.02 events/subject-year in the placebo + BR group. Four subjects (1.9%) in the IDL + BR group had their IDL dose reduced, 16 subjects (7.7%) in the IDL + BR group and 2 subjects (1.0%) in the placebo + BR group had an interruption in study drug, and 4 subjects (1.9%) in the IDL + BR group discontinued IDL due to ≥ Grade 3 diarrhea and/or colitis. No deaths due to diarrhea or colitis were reported.

A total of 7 subjects (3.4%) in the IDL + BR group and 2 subjects (1.0%) in the placebo + BR group had pneumonitis of any grade. The exposure-adjusted incidence rate for any grade pneumonitis was 0.02 events/subject-year in the IDL + BR group versus 0.01 events/subject-year in the placebo + BR group. Two subjects (1.0%) in the IDL + BR group and no subject in the placebo + BR group discontinued the study drug due to pneumonitis. One subject (0.5%) in the IDL + BR group had a dose reduction due to pneumonitis, and 1 subject (0.5%) each in the IDL + BR and placebo + BR groups had an interruption of study drug due to pneumonitis. One death was reported in the IDL + BR group which was attributed to the SAE of pneumonitis; the event began on Study Day 466.

A total of 13 subjects (6.3%) in the IDL + BR group and no subject in the placebo + BR group had ≥ Grade 3 rash by MST. The exposure-adjusted incidence rate for ≥ Grade 3 rash by MST was 0.05 events/subject-year in the IDL + BR group. A total of 2 subjects (1.0%) had their study drug dose reduced, 4 subjects (1.9%) had an interruption in study drug, and 3 subjects (1.4%) discontinued the study drug (IDL) due to ≥ Grade 3 rash by MST in the IDL + BR group. One death was reported in the IDL + BR group which was attributed to the SAE of SJS; the event began on Study Day 14.

A total of 108 subjects (52.2%) in the IDL + BR group and 60 subjects (28.7%) in the placebo + BR group had ≥ Grade 3 infection. The exposure-adjusted incidence rate for ≥ Grade 3 infection was 0.55 events/subject-year in the IDL + BR group versus 0.32 events/subject-year in the placebo + BR group. In the IDL + BR group, 5 subjects (2.4%) had their study drug dose reduced, 36 subjects (17.4%) had an interruption in study drug, and 18 subjects (8.7%) discontinued the study drug (IDL) due to ≥ Grade 3 infection. In the placebo + BR group, 1 subject (0.5%) had their study drug dose reduced, 12 subjects (5.7%) had an interruption in study drug, and 13 subjects (6.2%) discontinued the study drug (placebo) due to ≥ Grade 3 infection. A total of 14 subjects (6.8%) in the IDL + BR group and 10 subjects (4.8%) in the placebo + BR group died due to ≥ Grade 3 infections.

An imbalance in the incidence of ≥ Grade 3 febrile neutropenia was observed in this study: 49 subjects (23.7%) in the IDL + BR group and 13 subjects (6.2%) in the placebo + BR group experienced this AE. The exposure-adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.20 events/subject-year in the IDL + BR group and 0.06 events/subject-year in the placebo + BR group. In the IDL + BR group, 2 subjects (1.0%) had their study drug dose reduced, 15 subjects (7.2%) had an interruption in study drug, and 3 subjects (1.4%) discontinued the study drug (IDL) due to ≥ Grade 3 febrile neutropenia. In the placebo + BR group, 3 subjects (1.4%) had an interruption in study drug, no subject had their study drug dose reduced, and 2 subjects (1.0%) discontinued due to ≥ Grade 3 febrile neutropenia. One death in the placebo + BR group was attributed to the SAE of febrile neutropenia.

A total of 13 subjects (6.3%) in the IDL + BR group and 3 subjects (1.4%) in the placebo + BR group had CMV of any grade. The exposure-adjusted incidence rate for any grade CMV was 0.05 events/subject-year in the IDL + BR group and 0.01 events/subject-year in the placebo + BR group. One subject (0.5%) in the IDL + BR group had a dose reduction, 1 subject (0.5%) in the placebo + BR group had an interruption in study drug, and 1 subject (0.5%) each in the IDL + BR group and placebo + BR group discontinued study drug due to Grade 4 CMV and Grade 5 CMV, respectively. One death was reported in the placebo + BR group which was attributed to the SAE of CMV.

A total of 4 subjects (1.9%) in the IDL + BR group and no subject in the placebo + BR group had PJP of any grade. The exposure-adjusted incidence of any grade PJP was 0.01 events/subject-year in the IDL + BR group. No subject had a dose reduction or discontinued study drug (IDL/placebo) due to PJP; 2 subjects (1.0%) in the IDL + BR group had an interruption in study drug due to PJP. One death was reported in the placebo + BR group which was attributed to the SAE of pneumocystis pneumonia (death occurred later than 30 days following end of study).

Laboratory Evaluations of Interest: Laboratory evaluations of interest for IDL include neutropenia and transaminase elevations.

In this study, 89.9% (186 subjects) of the IDL + BR group were reported to have a decreased postbaseline neutrophil count of any grade: 21.7% (45 subjects) had decreases of Grade 3 and 106 subjects (51.2%) of Grade 4. In the placebo + BR group, 90.0% (188 subjects) had decreased postbaseline neutrophil count of any grade: 29.7% (62 subjects) had decreases of Grade 3 and 70 subjects (33.52%) of Grade 4. The exposure-adjusted incidence rate of laboratory abnormalities of any grade neutropenia was 3.95 events/subject-year in the IDL + BR group and 3.98 events/subject-year in the placebo + BR group. Median neutrophil counts were generally stable over time in both treatment groups.

In this study, 63.3% (131 subjects) of the IDL + BR group had treatment-emergent ALT laboratory abnormalities of any grade (21.3% [44 subjects] with ≥ Grade 3 abnormalities), compared with 32.1% (67 subjects) of the placebo + BR group (2.9% [6 subjects] with ≥ Grade 3 abnormalities). For AST, 53.6% (111 subjects) of the IDL + BR group had treatment-emergent abnormalities of any grade (15.5% [32 subjects] with ≥ Grade 3 abnormalities), compared with 29.2% (61 subjects) of the placebo + BR group (3.3% [7 subjects] with ≥ Grade 3 abnormalities). A total of 22.7% (47 subjects) of the IDL + BR group had treatment-emergent Grade 3 or 4 ALT and/or AST increases, compared with 3.8% (8 subjects) of the placebo + BR group. The exposure-adjusted incidence rate of treatment-emergent laboratory abnormalities of any grade ALT increase was 0.92 events/subject-year in the IDL + BR group and 0.40 events/subject-year in the placebo + BR group. The exposure-adjusted incidence rate of treatment-emergent laboratory abnormalities of any grade AST increase was 0.71 events/subject-year in the IDL + BR group and 0.36 events/subject-year in the placebo + BR group. AEs of ALT increased, transaminases increased, and hepatocellular injury led to discontinuation of IDL treatment for 0.5% (1 subject), 0.5% (1 subject), and 1.4% (3 subjects), respectively, of the IDL + BR group.

For the 47 subjects in the IDL + BR group with Grade 3 or 4 ALT and/or AST elevations, the median (minimum, maximum) time to onset of these events was 7.9 (2.1, 87.9) weeks. Forty-four of the 47 subjects (93.6%) had a median (minimum, maximum) time to resolution of 4.1 (1.1, 16.7) weeks. The 3 subjects without resolution discontinued from study treatment: 1 due to PD, 1 due to the AE of hepatocellular injury, and 1 due to withdrawal of consent. Thirty-five of the 47 subjects (74.5%) in the IDL + BR group with elevations were rechallenged with IDL after dose interruptions due to Grade 3 or 4 ALT and/or AST elevations. Twenty-three of the 35 subjects were rechallenged at IDL 150 mg twice daily, 5 of these 23 subjects had a recurrence of Grade 3 or 4 elevated ALT and/or AST, and 4 of these 5 subjects' elevated ALT and/or AST resolved to ≤ Grade 1. Twelve of the 35 subjects were rechallenged at IDL 100 mg twice daily, 4 of these 12 subjects had a recurrence of Grade 3 or 4 elevated ALT and/or AST, and all 4 of these subjects' elevated ALT and/or AST resolved to ≤ Grade 1.

Three subjects in the IDL + BR group and 1 subject in the placebo + BR group reported AST or ALT > 3 × ULN with concurrent elevation of bilirubin > 2 × ULN and approximately normal alkaline phosphatase levels. In the IDL + BR group, 2 subjects continued on IDL and are ongoing in the study at the time of this report, and 1 subject discontinued due to AEs. The subject in the placebo + BR group discontinued due to PD.

Deaths: Through the 02 May 2016 data cutoff date, 124 subject deaths were reported, 65 during the study and 59 during long-term follow-up. In the IDL + BR group, 53 subjects died (note, 1 subject died after withdrawal of consent), including 33 subjects who died on study (deaths between randomization and within 30 days following end of study) and 20 subjects who died during long-term follow-up. In the placebo + BR group, 71 subjects died, including 32 subjects who died on study and 39 subjects who died during long-term follow-up.

SAEs: Serious AEs were common in both treatment groups, reported for 71.0% (147 subjects) of the IDL + BR group and 45.0% (94 subjects) of the placebo + BR group. Serious AEs were typical of the population, with events occurring most commonly in the SOC of infections and infestations (41.5% [86 subjects] of the IDL + BR group and 23.4% [49 subjects] of the placebo + BR group) followed by blood and lymphatic system disorders (24.2% [50 subjects] of the IDL + BR group and 12.4% [26 subjects] of the placebo + BR group).

The most frequently reported SAEs by PT were as follows:

- IDL + BR group: febrile neutropenia (20.8%, 43 subjects), pneumonia (17.4%, 36 subjects), and pyrexia (12.1%, 25 subjects)
- Placebo + BR: pneumonia (7.7%, 16 subjects), pyrexia (5.3%, 11 subjects), and febrile neutropenia (4.8%, 10 subjects)

AEs Leading to Discontinuation of Study Drug: Overall, 32.9% (68 subjects) of the IDL + BR group and 14.8% (31 subjects) of the placebo + BR group discontinued study drug (IDL/placebo) due to an AE. Pneumonia led to study drug discontinuation in 5.3% (11 subjects) of the IDL + BR group and 2.4% (5 subjects) of the placebo + BR group, pyrexia led to study drug discontinuation in 1.9% (4 subjects) of the IDL + BR group and 1.0% (2 subjects) of the placebo + BR group, and diarrhea led to study drug discontinuation in 2.4% (5 subjects) of the IDL + BR group and no subject in the placebo + BR group.

Clinical Laboratory Evaluations: Hemoglobin concentrations and platelet counts trended upward with time for both treatment groups. Median neutrophil counts were generally stable over time in both treatment groups. The adjusted rates of hematologic abnormalities (all grades) were similar between the 2 treatment groups. The adjusted rates of chemistry abnormalities (all grades) were generally higher in the IDL + BR group most notably for elevations in alkaline phosphatase, ALT, AST, GGT, and cholesterol.

CONCLUSIONS:

This Phase 3, randomized, double-blind, placebo-controlled study met the primary endpoint of PFS as assessed by the IRC, as well the prespecified secondary endpoints of ORR, LNR rate, and OS. The overall conclusions from this interim analysis are as follows:

- The primary endpoint, PFS, was superior in the IDL + BR group compared to the placebo + BR group, with an adjusted HR (95% CI) of 0.33 (0.25, 0.44) and 2-sided p-value of < 0.0001 based on a stratified log-rank test. The median (95% CI) PFS was 20.8 (16.6, 26.4) months for subjects in the IDL + BR group and 11.1 (8.9, 11.1) months for subjects in the placebo + BR group. PFS following treatment with IDL + BR was improved compared to treatment with placebo + BR in all prespecified subgroups, including subjects with 17p deletion and/or TP53 mutation, subjects with mutated or unmutated IGHV, relapsed and refractory subjects, males, females, subjects < 65 years, subjects ≥ 65 years, whites, and nonwhites.
- The secondary endpoints evaluating ORR and LNR rate were also superior in the IDL + BR group compared with the placebo + BR group. The ORR (95% CI) was 70.0% (63.3, 76.2) for the IDL + BR group and 45.0% (38.1, 52.0) for the placebo + BR group, and the corresponding odds ratio (95% CI) was 3.09 (2.02, 4.72; p < 0.0001). The LNR rate (95% CI) was 96.9% (93.3, 98.8) for the IDL + BR group and 60.9% (53.7, 67.8) for the placebo + BR group, and the corresponding stratified odds ratio (95% CI) was 28.72 (10.48, 78.72; p < 0.0001). Results favoring IDL + BR over placebo + BR were demonstrated across all prespecified subgroups.
- The secondary endpoint of OS also met statistical significance between the IDL + BR group and placebo + BR group for both the 07 October 2015 and 02 May 2016 data cutoff dates: hazard ratios of 0.62 (p-value from stratified log-rank test = 0.0309) and 0.67 (p-value from stratified log-rank test = 0.0364), respectively. OS results favoring IDL + BR over placebo + BR were demonstrated in subjects with 17p deletion and those with 17p deletion and/or TP53 mutation.
- The most common AEs in the IDL + BR group were neutropenia, pyrexia, and diarrhea, all known adverse drug reactions of IDL. The most common AEs in the placebo + BR group were neutropenia, nausea, and pyrexia.
- ALT elevations occurred at an increased frequency in the IDL + BR group. These elevations generally resolved in approximately 4 weeks. AEs of ALT increased, transaminases increased, and hepatocellular injury led to discontinuation of IDL treatment for 1.0% (2 subjects), 0.5% (1 subject), and 1.4% (3 subjects), respectively, in the IDL + BR group.
- Febrile neutropenia and other infections (including serious infections) were more common in the IDL + BR group compared to the placebo + BR group.
- Overall, the efficacy and safety findings in this study demonstrate that the significant benefit outweighs the risk for the use of IDL, an oral PI3Kδ pathway inhibitor, in combination with BR in this population of subjects with relapsed CLL.