FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (Zydelig®, GS-1101)
Dose and Formulation:	Idelalisib 150 mg taken orally twice daily
Indication:	Chronic lymphocytic leukemia
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-312-0119
Phase of Development:	Phase 3
IND No.:	101254
EudraCT No.:	2012-001236-65
ClinicalTrials.gov Identifier:	NCT01659021
Study Start Date:	04 December 2012 (First Subject Screened)
Study End Date:	15 January 2015 (Last Subject Observation for the Primary Endpoint) 15 August 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Jennifer R. Brown, MD, PhD Affiliation: Dana Farber Cancer Institute
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Report Date:	12 February 2019
Previous Report Date(s):	21 April 2015 15 November 2016 04 December 2017

STUDY SYNOPSIS
Study GS-US-312-0119
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

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

Investigators: Multicenter study

Study Centers: 81 sites in the United States, Canada, Belgium, Denmark, France, Ireland, Poland, Spain, Sweden, United Kingdom, and Australia

Publications:

Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol 2017; 4 (3): e114–26.

Jones J, Robak T, Wach M, Brown JR, Menter AR, Vandenberghe E, et al. Updated results of a phase 3 randomized, controlled study of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukemia (CLL) [Poster 7515]. American Society of Clinical Oncology (ASCO) 52nd Annual Meeting; 2016 02 - 06 June; Chicago, IL.

Jones JA, Wach M, Robak T, Brown JR, Menter AR, Vanderberghe E, et al. Results of a Phase 3 Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (IDELA) in Combination with Ofatumumab (OFA) for Previously Treated Chronic Lymphocytic Leukemia (CLL) [Poster 7023]. American Society of Clinical Oncology (ASCO) 51st Annual Meeting; 2015 29 May - 02 June; Chicago, IL.

Robak T, Jones J, Wach M, Brown JR, Menter AR, Vandenberghe E, et al. Updated results of a phase 3 randomized, controlled study of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukemia (CLL) [Poster 213]. 21st Congress of the European Hematology Association (EHA); 2015 09-12 June; Copenhagen, Denmark.

Robak T, Wach M, Jones J, Owen C, Brown J, Menter A, et al. Results Of A Phase 3 Randomized Controlled Study Evaluating The Efficacy And Safety Of Idelalisib (Idela) In Combination With Ofatumumab (Ofa) For Previously Treated Chronic Lymphocytic Leukemia (CLL) [Poster LB598]. 20th Congress of the European Hematology Association (EHA); 2015 11-14 June; Vienna, Austria.

Flinn I, Kimby E, Cotter FE, Giles FJ, Janssens A, Pulczynski EJ, et al. A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia (CLL) [Poster TPS7131]. American Society of Clinical Oncology (ASCO); 2013 May 31-June 4; Chicago, IL.

Study Period:

04 December 2012 (First Subject Screened)
15 January 2015 (Last Subject Observation for the Primary Endpoint)
15 August 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To evaluate the effect of the addition of idelalisib (GS-1101, Zydelig®; IDL) to ofatumumab (Arzerra®) on progression-free survival (PFS) in subjects with previously treated chronic lymphocytic leukemia (CLL)

The secondary objectives of this study were as follows:

- To evaluate the effect of the addition of IDL to ofatumumab on the onset, magnitude, and duration of tumor control
- To evaluate the effect of the addition of IDL to ofatumumab on the onset, magnitude, and duration of tumor control for subjects with 17p deletion and/or TP53 mutation
- To assess the effect of the addition of IDL to ofatumumab 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 IDL to ofatumumab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to IDL
- To characterize the effect of ofatumumab on IDL exposure through the evaluation of IDL plasma concentrations over time
- To describe the safety profile observed with the addition of IDL to ofatumumab
- To estimate health resource utilization associated with the addition of IDL to ofatumumab

Methodology: Study GS-US-312-0119 was a global Phase 3, multicenter, randomized, open-label, parallel-group clinical 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 2:1 ratio to receive either IDL + ofatumumab combination therapy (Group A) or ofatumumab single-agent therapy (Group B).

Subjects who received combination therapy in Group A took IDL orally, twice daily, continuously.

All subjects received a maximum of 12 ofatumumab infusions. Ofatumumab was administered intravenously in the clinic starting at a dose of 300 mg on Day 1 (Week 1) (Groups A and B) and was continued with a dose of either 1000 mg (Group A) or 2000 mg (Group B) on Day 8

(Week 2), Day 15 (Week 3), Day 22 (Week 4), Day 29 (Week 5), Day 36 (Week 6), Day 43 (Week 7), Day 50 (Week 8), Day 78 (Week 12), Day 106 (Week 16), Day 134 (Week 20), and Day 162 (Week 24).

Subjects in Group A continued treatment with IDL or ofatumumab as scheduled, even if the other drug had to be discontinued due to toxicity.

Following permanent discontinuation of study drug(s), subjects remained on study until definitive progression of CLL or withdrawal from the study.

Number of Subjects (Planned and Analyzed):

Planned: 255 subjects (approximately 170 subjects to receive IDL + ofatumumab and 85 subjects to receive ofatumumab only)

Analyzed: 261 subjects (174 subjects assigned to IDL + ofatumumab and 87 subjects to ofatumumab alone; of these, 2 subjects [1 in each treatment group] did not receive treatment and therefore were not included in safety analyses)

Diagnosis and Main Criteria for Inclusion:

The target population consisted of adults with previously treated recurrent CLL who had measurable lymphadenopathy, required treatment for CLL, had disease that was not refractory to ofatumumab, and had experienced CLL progression < 24 months since the completion of the last prior treatment. 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 warranted treatment (consistent with accepted IWCLL criteria for initiation of therapy)
- Presence of radiographically measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter and ≥ 1.0 cm in the longest perpendicular diameter as assessed by computed tomography or magnetic resonance imaging [MRI])
- Prior treatment for CLL comprising therapy with either of the following, given alone or in combination:
  - A purine analog (eg, fludarabine, pentostatin, cladribine) administered for ≥ 2 cycles of cytotoxic treatment or
  - Bendamustine administered for ≥ 2 cycles of treatment
- Documentation of CLL progression < 24 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 ≥ 6 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, 2, 3, or 4 permitted])
- Karnofsky performance score of ≥ 60

Duration of Treatment:

Idelalisib was taken continuously until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable IDL-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Ofatumumab was administered until the earliest of a maximum of 12 infusions, subject withdrawal from study, definitive progression of CLL, intolerable ofatumumab-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Subjects in Group A continued with IDL or ofatumumab, even if the other drug had to be discontinued due to toxicity.

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

Group A: IDL 150 mg taken orally twice daily starting on Day 1 and taken continuously thereafter.

The batch numbers of IDL administered in this study were as follows:

- Idelalisib 150 mg: CV1110D2; CV1204B1; CV1303B1; CV1308B1; NSZV; THSP
- Idelalisib 100 mg: CV1107B2; CV1110C2; CY1201B1; CV1301C1; NSZS; PCZC; WWXH

Reference Therapy, Dose, and Mode of Administration:

Ofatumumab 300 mg intravenously on Day 1 (Week 1) (Groups A and B); thereafter 1000 mg (Group A) or 2000 mg (Group B) intravenously

The batch numbers of ofatumumab administered in this study were as follows:

- Ofatumumab 100 mg: C491830, C609415, C555607, C554191, and C574764
- Ofatumumab 1000 mg: C530265, C556810, C607757, C621696, C580638, and C598644

Batches C554191, and C574764, C580638, and C598644 were commercially available ofatumumab.

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 was CLL progression based on standard criteria other than lymphocytosis alone

Secondary Endpoints:

Five endpoints were designated as secondary endpoints for which sequential testing was performed to control Type I error rate. Secondary endpoints listed in the order of testing were overall response rate (ORR), lymph node response (LNR) rate, OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation, and complete response (CR) rate. All other endpoints were considered exploratory.

- ORR - defined as the proportion of subjects who achieved a CR or partial response (PR) and maintained their response for at least 8 weeks (with a 1-week window)
- 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 per independent review committee (IRC) assessments
- OS - defined as the interval from randomization to death from any cause during the study
- PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation - defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause
- CR rate - defined as the proportion of subjects who achieved a CR and maintained their response for at least 8 weeks (± 1 week)

Exploratory Endpoints:

- Time to response (TTR) - defined as the interval from randomization to the first documentation of confirmed CR or PR for subjects who responded with confirmed CR or PR
- Duration of response (DOR) - defined as the interval from the first documentation of confirmed 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 from baseline 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 to ≤ 18 cm by imaging, or regression to a liver LVD of ≤ 15 cm by physical examination
- 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
- 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)
- 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)
- 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

- Change from baseline in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) questionnaire
- Changes in performance status as documented using the Karnofsky performance criteria
- Change from baseline in overall health and single-item dimension scores as assessed using the EuroQoL Five-Dimension (EQ-5D) utility measure
- Changes from baseline in phosphatidylinositol 3-kinase (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
- 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)

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).

Statistical Methods:

Efficacy:

An 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.

Two formal interim analyses were planned for this study, the first after approximately 65 PFS events occurred (50% of planned events) and the second after 97 PFS events (75% of planned events) occurred. The prespecified significance level for the first interim analysis was 0.003 and for the second interim analysis was 0.018, using the O'Brien-Fleming alpha spending function.

By the date projected for the first interim analysis, when 50% of PFS events were estimated to have occurred, the actual number of PFS events approached the number of PFS events targeted for the second interim analysis (75% PFS events); therefore, a single interim analysis was conducted at this point at a significance level of 0.018, and a decision was made to continue the study until the final analysis.

The primary efficacy analysis reported in the GS-US-312-0119 Primary Analysis Clinical Study Report (CSR; dated 21 April 2015) was the planned final analysis based on 130 PFS events. The results reported in this Interim 3 CSR reflect approximately 27.5 months of additional follow-up data compared with the Primary Analysis CSR.

The Gilead Sciences, Inc. (Gilead) GS-US-312-0119 study team remained blinded to any integrated summary by treatment group throughout the study until the database was locked and unblinded for the primary analysis. The data monitoring committee reviewed unblinded interim efficacy results and made recommendations per prespecified efficacy boundaries.

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 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 did not die 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: null hypothesis (H_0): hazard ratio (HR) for PFS (between Group A [IDL + ofatumumab] and Group B [ofatumumab]) equals 1 versus alternative hypothesis (H_1): HR for PFS is less than 1. Progression-free survival 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.

Statistical Analysis of Secondary Endpoints:

Secondary efficacy endpoints included ORR, LNR rate, OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation, and CR rate.

In the primary efficacy analysis presented in the Primary Analysis CSR, 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 either at an interim or at the final analyses, the 5 secondary endpoints were to be tested sequentially at the 2-sided significance level of 0.03 in the order listed (ORR, LNR rate, OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation, and CR rate). If a null hypothesis in the sequence described above was not rejected, formal sequential testing was to be stopped, and only the nominal significance was to be cited for the remaining secondary endpoints. For the current interim report, there was no multiplicity control for the tests of the primary and secondary endpoints.

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

Differences in the LNR rate between the 2 treatment groups were compared using 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), which included all available survival information during the study with long-term follow-up to the data cutoff date of 02 May 2017. Data from surviving subjects were censored at the last time that the subject was known to be alive on study. 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.

PFS was compared between the 2 treatment groups based on the ITT Analysis Set with the subgroup of subjects with 17p deletion and/or TP53 mutation using the unstratified log-rank test.

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 Karnfosky 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 or PR and maintained the response for at least 8 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 antitumor therapy were included. Waterfall plots of best on-study percent change in SPD were provided for each treatment group using IRC data.

Differences between treatment groups for splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate, and neutrophil response rate were compared using CMH Chi-square tests after adjusting for stratification factors. For all analyses, odds ratios and the corresponding 95% CIs were presented.

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 mean of the change from baseline over time was plotted. Subjects with minimal important differences (MID) in the different subscales were analyzed by KM method, and the proportion of subjects with any improvement was summarized.

The Karnofsky performance status 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 US preference-weighted index. The mean and change from baseline in mean EuroQOL visual analog 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. Changes from baseline in EQ VAS scores and EQ-5D summary index were analyzed using a mixed-effects model by including treatment, time, treatment-by-time interaction, and stratification factors as fixed effects. The least squares of mean change from baseline over time were plotted.

Exposure:

No pharmacokinetic analyses were performed for this report.

Safety:

All AEs were listed. The focus of AE summarization was on treatment-emergent adverse events (TEAEs). A TEAE was defined as an AE that occurred or worsened in the period from the first dose of study treatment (IDL and/or ofatumumab) to 30 days after the last dose of study drug.

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. 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], high-level term [HLT], and preferred term [PT]) were provided by treatment groups for the following: AEs; AEs by CTCAE grade; ≥ Grade 3 AEs; IDL-related AEs; ofatumumab-related AEs; SAEs; IDL- and ofatumumab-related SAEs; AEs leading to IDL reduction and/or interruption, IDL interruption, or IDL reduction; AEs leading to ofatumumab delay; AEs leading to discontinuation of IDL or ofatumumab; AEs leading to death; and AE incidence rates adjusted for total exposure. For the analysis of incidence rate adjusted for total exposure, the total exposure time of all subjects (T) was calculated as $T = \Sigma\ t_i$ where t_i was the i^{th} subject's exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

SUMMARY OF RESULTS:

For Study GS-US-312-0119, there were 3 interim CSRs. The Primary Analysis CSR examined data up to 15 January 2015; 90 subjects were ongoing in the study for this interim report. For the Interim 2 CSR, data up to 02 May 2016 were examined; 35 subjects were ongoing in the study for the second interim report. For the Interim 3 CSR, data up to 02 May 2017 were examined; 23 subjects were ongoing in the study for the third interim report. This report is the final clinical study report for this study.

Subject Disposition, Exposure, Demographics, and Baseline Characteristics:

A total of 261 subjects were randomized in a 2:1 ratio (174 subjects in the IDL + ofatumumab group and 87 subjects in the ofatumumab alone group). Of these 261 randomized subjects, 1 subject in each group withdrew from the study prior to study treatment due to either physician or subject decision. Thus, 261 subjects were included in the ITT Analysis Set, and 259 subjects were included in the Safety Analysis Set.

A total of 173 subjects received treatment with IDL + ofatumumab. Forty seven subjects (27.0%) met the primary endpoint; 40 subjects (23.0%) experienced disease progression and 7 subjects (4.0%) experienced death. A total of 126 subjects (72.4%) discontinued treatment for other reasons and without meeting the primary endpoint. The investigators cited AEs as the reason for discontinuation from treatment in 45.4% (79 subjects) of the IDL + ofatumumab group.

Overall, the investigators assessed that the primary study endpoint of disease progression or death had been met by 57.5% (150 subjects) of the total study population, including 57.5% (100 subjects) of the IDL + ofatumumab group and 57.5% (50 subjects) of the ofatumumab alone group. Overall, 42.5% (111 subjects) of the total study population discontinued the study without meeting the primary endpoint (42.5% [74 subjects] of the IDL + ofatumumab group and 42.5% [37 subjects] of the ofatumumab alone group). In the IDL + ofatumumab group, the primary reasons for discontinuation were physician decision (19.5% [34 subjects]) and withdrawal by the subject (10.9% [19 subjects]). In the ofatumumab alone group, the primary reasons for discontinuation were physician decision and withdrawal by the subject (each in 18.4% [16 subjects]).

Overall, the demographics and baseline characteristics (age, sex, race, body mass index [BMI]) were generally comparable between the 2 treatment groups. Most subjects (64.0%) were ≥ 65 years of age, with a median (Q1, Q3) age of 68 (61, 74) years, and an age range of 36 to 85 years. Most subjects (71.3%) were male and most were white (84.3%). Almost all subjects (226 subjects; 86.6%) had a reduced Karnofsky performance status (KPS) at study entry: 67.5% had modest reduction (ie, KPS score 80 to 90), 19.1% had significant reduction (ie, KPS score 60 to 70). The subject population had presented with CLL for an extensive period prior to study entry: the median (Q1, Q3) time since diagnosis was 7.7 (4.8, 10.8) years (92.8 [57.1, 129.2] months), with a range of 6.7 to 351.8 months. At study screening, most subjects had advanced disease, with 63.6% Rai Stage III or IV and 58.2% Binet Stage C. Disease characteristics were balanced between treatment groups. In the total population at screening, 55.6% of the subjects had platelet counts $< 100 \times 10^9$/L, 46.9% of the subjects had hemoglobin < 11 g/dL, and 22.1% of the subjects had ANC $< 1.5 \times 10^9$/L; the median (Q1, Q3) cumulative illness rating scale score at screening was 4.0 (2.0, 7.0).

Efficacy Results:

Primary Endpoint:

Progression-Free Survival: The analysis of PFS, based on the ITT Analysis Set and stratified by 17p deletion and/or TP53 mutation, IGHV mutation, and disease status, showed that IDL + ofatumumab was superior to ofatumumab alone. A total of 67.8% (118 subjects) of the IDL + ofatumumab group and 65.5% (57 subjects) of the ofatumumab alone group experienced a PFS event, with an adjusted HR (95% CI) of 0.26 (0.18, 0.37) and 2-sided p-value of < 0.0001 based on a stratified log-rank test. The median (95% CI) PFS was 16.6 (13.7, 19.6) months in the IDL + ofatumumab group and 8.0 (5.7, 8.4) months in the ofatumumab alone group. Progression-free survival following treatment with IDL + ofatumumab was improved relative to treatment with ofatumumab in all predefined subgroups, including subjects with 17p deletion and/or TP53 mutation, subjects with mutated or unmutated IGHV, relapsed and refractory subjects, males and females, subjects < 65 years and ≥ 65 years, and whites and nonwhites.

Secondary Endpoints:

ORR: Based on the ITT Analysis Set, the ORR (classified as CR or PR with minimal duration of 8 weeks) (95% CI) was 75.3% (68.2%, 81.5%) for the IDL + ofatumumab group and 17.2% (10%, 26.8%) for the ofatumumab alone group. The odds ratio (95% CI) for the ORR was 16.85 (8.17, 34.76), which favored IDL + ofatumumab compared with ofatumumab alone ($p < 0.0001$).

LNR rate: Based on the ITT Analysis Set, the LNR rate (95% CI) was 92.7% (87.6%, 96.2%) for the IDL + ofatumumab group and 4.9% (1.4%, 12.2%) for the ofatumumab alone group. The stratified odds ratio (95% CI) for the LNR rate was 483.16 (94.63, 2467.02), which favored IDL + ofatumumab compared with ofatumumab alone ($p < 0.0001$).

OS: The OS analysis was performed using the ITT Analysis Set, which included all available survival information from Study GS-US-312-0119. A total of 127 subjects had died (87 subjects [50.0%] in the IDL + ofatumumab group and 40 subjects [46.0%] in the ofatumumab alone group). The adjusted HR (95% CI) for OS was 0.79 (0.54, 1.15); $p = 0.247$ based on a stratified log-rank test.

PFS in the Subgroup of Subjects with 17p Deletion and/or TP53 Mutation: In subjects with 17p deletion and/or TP53 mutation, the unadjusted hazard ratio (95% CI) for PFS was 0.30 (0.17, 0.51).

CR Rate: As there were only 2 CRs on study (both in the IDL + ofatumumab group), this analysis was not performed.

Exploratory Endpoints:

TTR: Among subjects who achieved a response (CR or PR), the median (Q1, Q3) TTR was 1.7 (1.6, 3.5) months for subjects treated with IDL + ofatumumab (N = 131) and 1.7 (1.6, 3.5) months for subjects treated with ofatumumab alone.

DOR: Among subjects who achieved a response (CR or PR), the median (95% CI) KM estimate of DOR was 18.1 months (14.8, 20.5) months for the IDL + ofatumumab group (N = 131) and 6.5 (5.6, 15.0) months for the ofatumumab alone group (N = 15).

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 –76.0 (−82.6, −65.3) for subjects treated with IDL + ofatumumab and –13.1 (−29.3, 0.1) for the ofatumumab alone group.

Efficacy Results by 17p Deletion and/or TP53 Mutation Status:

This study included 103 subjects with 17p deletion and/or TP53 mutation (70 in the IDL + ofatumumab group and 33 in the ofatumumab alone group). Efficacy results for subjects with 17p deletion and/or TP53 mutation and for subjects with neither 17p deletion nor TP53 mutation are summarized herein. In both groups, treatment with IDL + ofatumumab resulted in improved PFS, ORR, LNR rate, and DOR compared with ofatumumab alone. In addition, OS was improved in subjects with 17p deletion and/or TP53 mutation who were treated with IDL + ofatumumab compared with ofatumumab alone.

	Subjects with 17p Deletion and/or TP53 Mutation		**Subjects with Neither 17p Deletion nor TP53 Mutation**	
Endpoint (Measure)	**IDL + O (N = 70)**	**O (N = 33)**	**IDL + O (N = 104)**	**O (N = 54)**
PFS, HR (95% CI)	0.30 (0.17, 0.51)		0.32 (0.21, 0.49)	
ORR, odds ratio (95% CI)	15.03 (5.07, 44.6)		14.67 (6.43, 33.45)	
LNR rate, odds ratio (95% CI)	240 (28.16, 2045.52)		300.53 (68.91, 1310.66)	
OS, HR (95% CI)	0.5 (0.29, 0.87)		1.06 (0.62, 1.8)	
DOR, median (95% CI) months	14.8 (11.5, 20.4)	6.5 (4.7, 21.0)	20 (14.9, 29.2)	7.6 (5.4, 15.0)

Efficacy Results by 17p Deletion Status

This study included 66 subjects with 17p deletion (47 in the IDL + ofatumumab group and 19 in the ofatumumab alone group). Efficacy results for subjects with or without 17p deletion are summarized below. In both groups, treatment with IDL + ofatumumab resulted in improved PFS, ORR, LNR rate, and DOR compared with ofatumumab alone.

	Subjects with 17p Deletion		**Subjects without 17p Deletion**	
Endpoint (Measure)	**IDL + O (N = 47)**	**O (N = 19)**	**IDL + O (N = 127)**	**O (N = 68)**
PFS, HR (95% CI)	0.21 (0.09, 0.49)		0.31 (0.21, 0.45)	
ORR, odds ratio (95% CI)	15 (3.09, 72.92)		16.43 (7.82, 34.53)	
LNR rate, odds ratio (95% CI)	NEst (NEst – NEst)		213.5 (61.78, 737.84)	
OS, HR (95% CI)	0.56 (0.27, 1.13)		0.88 (0.56, 1.37)	
DOR, median (95% CI) months	14.1 (8.1, 20.4)	6.5 (NR, NR)	20 (14.9, 23.9)	7.6 (5.4, 21.0)

NEst = Not estimable as there were no responders in the ofatumumab alone group; NR = not reached

Pharmacokinetics Results: No pharmacokinetic or pharmacodynamic analyses were performed for this report.

Safety Results:

All safety analyses were performed on the Safety Analysis Set. The median (Q1, Q3) duration of exposure to IDL in the IDL + ofatumumab group was 13.9 (6.8, 25.6) months, with a range of 0.2 to 60.3 months. Ofatumumab exposure was reported in the Study GS-US-312-0119 Interim 3 CSR (Section 11.1) and there has been no additional ofatumumab exposure data to report since that time (02 May 2017). Of note, the overall duration of exposure to either drug (either IDL or ofatumumab) was longer in the IDL group, because IDL dosing could continue throughout the study while ofatumumab was limited to 12 doses. Additionally, because of the 2:1 randomization, the total exposure time (in subject-years) in the IDL + ofatumumab group was much longer than in the ofatumumab alone group. For this reason, some of the analyses of AEs are adjusted for exposure time.

Key safety findings are as follows:

AEs: TEAEs were common in both groups, occurring in 100.0% (173 subjects) of the IDL + ofatumumab group and 98.8% (85 subjects) of the ofatumumab alone group. The most commonly reported TEAEs by treatment group were as follows:

- Idelalisib + ofatumumab: diarrhea (57.8%, 100 subjects), pyrexia (39.3%, 68 subjects), and neutropenia (37.0%, 64 subjects)
- Ofatumumab alone: fatigue (27.9%, 24 subjects), nausea and infusion-related reaction (each 26.7%, 23 subjects), and diarrhea (24.4%, 21 subjects)

Of note, the longer duration on study in the IDL + ofatumumab group had an impact on the numbers of subjects reporting events. The AEs (any grade) with the highest incidence rates adjusted for exposure time by treatment group were as follows:

- Idelalisib + ofatumumab: diarrhea (0.60 events/person-year), neutropenia (0.35 events/person-year), and pyrexia (0.34 events/person-year)
- Ofatumumab alone: infusion-related reaction (0.94 events/person-year), fatigue (0.91 events/person-year), and nausea (0.89 events/person-year)

When comparing treatment groups, the adjusted rates of AEs were generally either similar in the 2 treatment groups or higher in the ofatumumab alone group. Among individual events (any grade) with an exposure-adjusted incidence rate ≥ 0.05 events/person-year, the only events with meaningfully higher adjusted rates in the IDL + ofatumumab group relative to the ofatumumab alone group were bronchitis (0.11 events/person-year in the IDL + ofatumumab group versus 0.00 events/person-year in the ofatumumab alone group), colitis (0.09 versus 0.00 events/person-year, respectively), dehydration (0.07 versus 0.00 events/person-year, respectively), productive cough (0.07 versus 0.00 events/person-year, respectively), oral candidiasis (0.06 versus 0.00 events/person-year, respectively), and rash maculo-papular (0.05 versus 0.00 events/person-year, respectively).

AEs by Severity:

Overall, ≥ Grade 3 AEs were reported in 94.8% (164 subjects) of the IDL + ofatumumab group and 55.8% (48 subjects) of the ofatumumab alone group. The exposure-adjusted incidence rate of ≥ Grade 3 AEs was 1.95 events/person-year in the IDL + ofatumumab group and 2.19 events/person-year in the ofatumumab alone group.

The most commonly reported ≥ Grade 3 AEs by treatment group were as follows:

- Idelalisib + ofatumumab: neutropenia (35.8%, 62 subjects), diarrhea (25.4%, 44 subjects), and pneumonia (17.3%, 30 subjects)
- Ofatumumab alone: neutropenia (16.3%, 14 subjects), pneumonia (8.1%, 7 subjects), and thrombocytopenia (7.0%, 6 subjects)

IDL-related AEs:

The most frequently reported AEs assessed by the investigator as related to IDL were diarrhea (43.9%, 76 subjects), neutropenia (22.0%, 38 subjects), and fatigue (19.7%, 34 subjects).

Adverse Events of Interest (AEI):

The AEI for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade pneumonitis, any grade PML, ≥ Grade 3 rash by MST, ≥ Grade 3 ALT/AST/transaminases increased (discussed below in Laboratory Evaluations of Interest), and Richter's transformation and secondary malignancies. Following from safety findings identified in March 2016, the AEI list was expanded to include infection (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade cytomegalovirus [CMV] infection, any grade PJP). Gilead's ongoing pharmacovigilance and signal detection practices for Zydelig (idelalisib) prompted the addition of any grade organizing pneumonia as of September 2017.

Bowel perforation: In the study overall, 2 subjects experienced a bowel perforation: 1 subject (0.6%) in the IDL + ofatumumab group and 1 subject (1.2%) in the ofatumumab alone group.

Diarrhea/colitis: For the AEs of diarrhea and/or colitis, the analysis utilized the combined PTs of diarrhea and colitis. In the study overall, 29.5% (51 subjects) of the IDL + ofatumumab group reported ≥ Grade 3 diarrhea and/or colitis compared with 1.2% (1 subject) of the ofatumumab alone group. The adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.21 events/person-year in the IDL + ofatumumab group versus 0.03 events/person-year in the ofatumumab alone group. In the IDL + ofatumumab group, the median (Q1, Q3) time to onset of the first ≥ Grade 3 event of diarrhea/colitis was 47.7 (23.7, 81.1) weeks, and the median (Q1, Q3) time to resolution of the highest ≥ Grade 3 diarrhea/colitis (N = 47) was 2.4 (1.1, 4.7) weeks. In the study overall, 14 subjects in the IDL + ofatumumab group discontinued IDL due to ≥ Grade 3 diarrhea/colitis and no deaths due to diarrhea or colitis were reported.

PML: In the study overall, no subjects in the IDL + ofatumumab group reported PML compared with 2 subjects (2.3%) in the ofatumumab alone group.

Pneumonitis: In the study overall, there were 10 subjects (5.8%) in the IDL + ofatumumab group with pneumonitis (preferred term). In addition, 2 subjects (7570-15440 and 7915-16301) experienced "interstitial pneumonitis" (verbatim term) which, per MedDRA coding convention was coded to the PT "interstitial lung disease," and 8 subjects (4.6%) reported pneumonitis of ≥ Grade 3 in severity. In the ofatumumab alone group, no subjects reported pneumonitis. Five subjects (which includes a subject with "interstitial lung disease") in the IDL + ofatumumab group discontinued IDL due to pneumonitis; the events resolved following study drug discontinuation in 4 of these 5 subjects. Overall, there was 1 death due to pneumonitis; this event was considered related to IDL by the investigator.

Rash by MST: In the study overall, 5.8% (10 subjects) reported rash MST of ≥ Grade 3 in severity. In the ofatumumab alone group, 2.3% (2 subjects) reported rash MST of ≥ Grade 3 in severity. There were no Grade 4 (ie, life-threatening) or Grade 5 (ie, death) events of rash in either treatment group. The adjusted incidence rate for ≥ Grade 3 rash MST was 0.04 events/person-year in the IDL + ofatumumab group versus 0.06 events/person-year in the ofatumumab alone group.

Infections: In the study overall, ≥ Grade 3 infection was reported in 46.8% (81 subjects) of the IDL + ofatumumab group and in 30.2% (26 subjects) of the ofatumumab alone group. The adjusted incidence rate for ≥ Grade 3 infection was 0.40 events/person-year in the IDL + ofatumumab group and 0.92 events/person-year in the ofatumumab alone group.

Febrile neutropenia: In the study overall, ≥ Grade 3 febrile neutropenia was reported in 13.3% (23 subjects) of the IDL + ofatumumab group and in 3.5% (3 subjects) of the ofatumumab alone group. The adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.09 events/person-year in both treatment groups.

Cytomegalovirus: In the study overall, CMV infection was reported for 1.7% (3 subjects) of subjects in the IDL + ofatumumab group compared with no subjects in the ofatumumab alone group.

PJP: In the study overall, PJP was reported in 6.4% (11 subjects) of the IDL + ofatumumab group and in 1.2% (1 subject) of the ofatumumab alone group. The adjusted incidence rate for PJP was 0.04 events/person-year in the IDL + ofatumumab group and 0.03 events/person-year in the ofatumumab alone group.

Organizing Pneumonia: No subjects in either treatment group reported organizing pneumonia in this study.

Richter's transformation and secondary malignancies: Exposure-adjusted rates for Richter's transformation and secondary malignancies were higher in the ofatumumab alone than in the IDL + ofatumumab group (Richter's transformation 0.12 vs 0.02 and secondary malignancies 0.26 vs 0.12 events/person-year, respectively). In the study overall, 16.8% (29 subjects) of the IDL + ofatumumab group and 9.3% (8 subjects) of the ofatumumab alone group reported a second malignancy.

Deaths:

In the study overall, 126 subjects died, including 47 during the study (defined as the study period + 30-day follow-up period for safety). In the IDL + ofatumumab group, 49.7% (86 subjects) died, including 22.5% (39 subjects) on study and 27.2% (47 subjects) during long-term follow-up (defined as later than the end of study + 30 days). In the ofatumumab alone group, 46.5% (40 subjects) died, including 9.3% (8 subjects) on study and 37.2% (32 subjects) during long-term follow-up. Although the percentage of subjects who died on study was greater in the IDL + ofatumumab group than in the ofatumumab alone group (22.5% vs 9.3%), the exposure-adjusted incidence rates were the same (0.13 person-years). The types of AEs leading to death also were consistent with a population with advanced CLL.

SAEs:

In the study overall, SAEs were common in both treatment groups, reported for 78.6% (136 subjects) of the IDL + ofatumumab group and 41.9% (36 subjects) of the ofatumumab alone group. Adjusting for exposure time, the incidence rate (95% CI) for SAEs was 0.90 (0.75, 1.06) per person-year in the IDL + ofatumumab group and 1.40 (0.98, 1.94) per person-year in the ofatumumab alone group. Serious AEs were typical of the population, with events occurring most commonly in the SOCs of infections and infestations (40.5% [70 subjects] of the IDL + ofatumumab group and 29.1% [25 subjects] of the ofatumumab alone group), blood and lymphatic system disorders (22.5% [39 subjects] of the IDL + ofatumumab group and 10.5% [9 subjects] of the ofatumumab alone group), and gastrointestinal disorders (24.3% [42 subjects] of the IDL + ofatumumab group and 4.7% [4 subjects] of the ofatumumab alone group). The most frequently reported SAEs by PT were pneumonia, pyrexia, and diarrhea in the IDL + ofatumumab group and pneumonia and febrile neutropenia in the ofatumumab alone group.

Idelalisib Discontinuations due to AEs:

In the study overall, 46.8% (81 subjects) of the IDL + ofatumumab group discontinued IDL due to an AE. Gastrointestinal disorders were the most common type of AE that led to discontinuation (15.6%, 27 subjects), predominantly including diarrhea (10.4%, 18 subjects) and colitis (4.0%, 7 subjects). Pneumonia led to IDL discontinuation in 5.2% (9 subjects) and pneumonitis led to discontinuation in 2.9% (5 subjects, which includes 1 subject with the verbatim term “interstitial pneumonitis” that was coded to the PT “interstitial lung disease”).

Laboratory Evaluations of Interest:

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

Neutropenia: In this study, 72.3% (125 subjects) of the IDL + ofatumumab group and 58.1% (50 subjects) of the ofatumumab alone group had treatment-emergent laboratory assessments of neutrophil count decreased. Overall, 49.7% (86 subjects) of the IDL + ofatumumab group and 32.6% (28 subjects) of the ofatumumab alone group had ≥ Grade 3 treatment-emergent neutrophil count decreases.

Transaminase Elevations: In the current study, laboratory assessments of ALT elevations occurred more commonly in subjects in the IDL + ofatumumab group compared with the ofatumumab alone group. Overall, 55.5% (96 subjects) of the IDL + ofatumumab group had treatment-emergent ALT laboratory abnormalities of any grade (11.6% [20 subjects] with ≥ Grade 3 abnormalities) compared with 20.9% (18 subjects) of the ofatumumab alone group (1.2% [1 subject] with ≥ Grade 3 abnormalities). For AST, 39.3% (68 subjects) of the IDL + ofatumumab group had treatment-emergent abnormalities of any grade (8.1% [14 subjects] with ≥ Grade 3 abnormalities) compared with 19.8% (17 subjects) of the ofatumumab alone group (1.2% [1 subject] with ≥ Grade 3 abnormalities).

In the 22 subjects in the IDL + ofatumumab group with Grade 3 or 4 ALT and/or AST elevations, the cumulative incidence function (CIF) median (95% CI) time to onset of these events was not reached. Seventeen of the 22 subjects (77.3%) had resolution of both ALT and AST to ≤ Grade 1 within 30 days of the last dose of study drug; the KM median (95% CI) time to resolution in these subjects was 3.1 (1.7, 5.1) weeks. (Of the 5 subjects with initial Grade 3 or 4 ALT and/or AST elevations that did not resolve within 30 days of the last dose of study drug, 1 had resolution later than 30 days past the last dose of study drug and 4 died.)

Fifteen of the 22 subjects with ALT and/or AST elevations (68.2%) were rechallenged with IDL after dose interruptions due to Grade 3 or 4 ALT/AST. Of these 15 subjects, 9 (60.0%) had recurrence of Grade 3 or 4 ALT/AST, and of these 9 subjects, 8 (88.9%) had subsequent resolution to ≤ Grade 1 within 30 days of the last dose of study drug. AEs within the HLT of liver function analyses (including ALT increased, AST increased, and transaminases increased) led to discontinuation of IDL treatment in 2.3% (4 subjects) of the IDL + ofatumumab group.

In the IDL + ofatumumab group, 1.2% (2 subjects) had AST or ALT > 3 × ULN with concurrent elevation of bilirubin > 2 × ULN. Both of these subjects satisfied the laboratory criteria for Hy's law (normal alkaline phosphatase with elevated bilirubin) and both cases were complicated by clinical courses of sepsis around the time of peak hepatic manifestations, suggesting a likely etiology for the laboratory abnormalities other than a causal association with study drug. No subjects in the ofatumumab alone group met the laboratory criteria for Hy's law.

Clinical Laboratory Evaluations:

Hemoglobin concentrations and platelet counts trended upward with time for both treatment groups; ANCs remained stable in both groups.

CONCLUSIONS:

The overall conclusions of the study are as follows:

- The safety and efficacy results presented in this report are consistent with those from the previous CSRs. Continued efficacy of IDL + ofatumumab was observed, and no new safety signals were identified.
- The primary endpoint, PFS, was superior in the IDL + ofatumumab group compared with ofatumumab alone, with an adjusted HR (95% CI) of 0.26 (0.18, 0.37) and 2-sided p-value of < 0.0001 based on a stratified log-rank test. The median (95% CI) PFS was 16.6 (13.7, 19.6) months for subjects in the IDL + ofatumumab group and 8.0 (5.7, 8.4) months for subjects in the ofatumumab alone group. Progression-free survival following treatment with IDL + ofatumumab was improved compared with treatment with ofatumumab in all predefined subgroups, including subjects with 17p deletion and/or TP53 mutation, subjects with mutated or unmutated IGHV, relapsed and refractory subjects, males and females, subjects < 65 years and ≥ 65 years, and whites and nonwhites.
- The secondary endpoints ORR and LNR rate were also superior in the IDL + ofatumumab group compared with the ofatumumab alone group. The ORR (95% CI) was 75.3% (68.2%, 81.5%) for the IDL + ofatumumab group and 17.2% (10%, 26.8%) for subjects in the ofatumumab alone group, and the corresponding odds ratio (95% CI) was 16.85 (8.17, 34.76); p < 0.0001. The LNR rate (95% CI) was 92.7% (87.6%, 96.2%) in the IDL + ofatumumab group and was 4.9% (1.4%, 12.2%) in the ofatumumab alone group, and the corresponding stratified odds ratio (95% CI) was 483.16 (94.63, 2467.02); p < 0.0001. Results favoring IDL + ofatumumab over ofatumumab alone were demonstrated across all subgroups.
- In the overall population, the hazard ratio (95% CI) for the secondary endpoint of OS between the IDL + ofatumumab group and the ofatumumab alone group was 0.79 (0.54, 1.15); p = 0.247.

- Among the subset of subjects with either 17p deletion or TP53 mutation, OS was improved in the IDL + ofatumumab group compared with the ofatumumab alone group (HR [95% CI] 0.5 [0.29, 0.87]; p = 0.0119 without multiplicity adjustment).
- Other endpoints (PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation, DOR, and best percentage change in SPD) also showed improvements in the IDL + ofatumumab group versus the ofatumumab alone group.
- In the subgroups of subjects with or without 17p deletion and/or TP53 mutation, as well as the subgroups with or without 17p deletion, treatment with IDL + ofatumumab resulted in improved PFS, ORR, LNR rate, and DOR compared with ofatumumab alone.
- No new safety concerns were identified in this study. The most common AEs in the IDL + ofatumumab group were diarrhea, pyrexia, and neutropenia, all known adverse drug reaction (ADRs) of IDL. The most common AEs in the ofatumumab alone group were fatigue, infusion-related reaction, nausea, and diarrhea.
- ALT elevations occurred at an increased frequency in the IDL + ofatumumab group. AEs within the HLT of liver function analyses (including ALT increased and AST increased) led to discontinuation of IDL treatment in 2.3% (4 subjects) of the IDL + ofatumumab group. Two subjects in the IDL + ofatumumab group met the laboratory criteria for Hy's law, although the cases were complicated by a clinical picture of sepsis.
- Overall, the efficacy and safety findings in this study continue to support a positive benefit-risk evaluation for the use of IDL, an oral, PI3K p110δ isoform (P13Kδ) inhibitor, in combination with ofatumumab in this population of subjects with relapsed CLL encompassing a range of fitness levels.