FINAL ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Obinutuzumab Compared to Chlorambucil in Combination with Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib (IDL, Zydelig®)
Dose and Formulation:	Idelalisib 150-mg tablets
Indication:	Chronic Lymphocytic Leukemia
Sponsor:	Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102 USA Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-312-0118
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	101254 2013-004551-20
ClinicalTrials.gov Identifier:	NCT01980875
Study Start Date:	21 April 2015 (First Subject Screened)
Study End Date:	13 May 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Wojciech Jurczak, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Ronald Dubowy, MD Telephone: PPD Fax: PPD
Report Date:	31 March 2017

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-312-0118
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Obinutuzumab Compared to Chlorambucil in Combination with Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia

Investigators: This was a global multicenter study.

Study Centers: A total of 65 active sites, with 18 sites that enrolled at least 1 subject in the following countries: Australia, Belgium, Canada, France, Poland, Spain, United Kingdom, and United States

Publications: None planned

Study Period:

21 April 2015 (First Subject Screened)
13 May 2016 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To evaluate the effect of the combination of idelalisib (IDL) and obinutuzumab (Obi) (IDL + Obi) versus the combination of chlorambucil (Ch) and Obi (Ch + Obi) on progression-free survival (PFS) in subjects with previously untreated chronic lymphocytic leukemia (CLL)

The secondary objectives of this study were as follows:

- To evaluate the effect of IDL + Obi versus Ch + Obi on the magnitude of response and overall survival (OS)
- To evaluate the effect of IDL + Obi versus Ch + Obi on minimal residual disease
- To describe the safety profile of IDL + Obi

Methodology:

Study GS-US-312-0118 was a Phase 3, international, multicenter, 2-arm, randomized, open-label, and active-controlled study. The aim of the study was to evaluate the efficacy and safety of IDL + Obi versus Ch + Obi in previously untreated CLL adult subjects who had measurable lymphadenopathy and were not candidates for standard-dose FCR therapy.

After a screening period of up to 28 days, eligible subjects were enrolled in an initial open-label safety run-in phase to evaluate the tolerability of IDL + Obi. Planned enrollment in the safety run-in was 6 to 9 subjects. Eight subjects were sequentially enrolled to ensure 4-week safety data were obtained for at least 6 subjects. Each subject received IDL + Obi treatment as per the treatment schedule for the randomized portion. Following the completion of 4 weeks of IDL + Obi treatment for the last enrolled safety run-in subject, safety data were reviewed by an independent data monitoring committee (DMC). The DMC recommended initiation of the randomized portion, with continued monitoring for neurologic events, transaminase elevations, and neutropenia.

In the randomized portion, subjects were stratified by 3 binary factors: (1) central laboratory determination of 17p deletion status (presence versus absence); (2) central laboratory determination of immunoglobulin heavy chain variable region gene (IgHV) mutation status in CLL cells (unmutated [or IgHV3-21] versus mutated [or indeterminate]); and (3) Rai Stage (0-II versus III–IV). Subjects were allocated in a 1:1 ratio using fixed block central randomization to the IDL + Obi or Ch + Obi treatment groups.

Subjects in the safety run-in and randomized IDL + Obi treatment groups received IDL twice daily continuously for 96 weeks along with 8 doses (4-week cycles) of Obi (Days 1 and 2 [split dose], Days 8 and 15 of Cycle 1, and Day 1 of Cycles 2 to 6) over 21 weeks. Clinic/laboratory visits occurred on Days 1, 2, 8, and 15 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of Cycles 3 to 6, every 4 weeks through Week 36, every 6 weeks through Week 48, every 8 weeks through Week 96, and every 12 weeks thereafter.

Subjects in the Ch + Obi treatment group received 12 doses of Ch administered every 14 days and 8 doses (4-week cycles) of Obi (Days 1 and 2 [split dose], Days 8 and 15 of Cycle 1, and Day 1 of Cycles 2 to 6) over 23 weeks. Clinic/laboratory visits occurred on Days 1, 2, 8 and 15 of Cycle 1, Day 1 of Cycle 2, and then every other week through Week 24. Subjects who continued on study after Week 24 had clinic visits every 4 weeks through Week 36, every 6 weeks through Week 48, every 8 weeks through Week 96, and every 12 weeks thereafter.

The duration of the screening period was up to 28 days, followed by a treatment period of up to 96 weeks for the IDL + Obi treatment group and 23 weeks for the Ch + Obi treatment group. The treatment duration with Obi and/or Ch was up to 21 and 23 weeks, respectively. Including long-term follow-up, the overall duration of the study was expected to be approximately 10 years.

Number of Subjects (Planned and Analyzed):

Planned: 306 to 309 subjects

Analyzed: 57 subjects

Diagnosis and Main Criteria for Inclusion:

The target population consisted of adult subjects who required treatment for previously untreated CLL, had measurable lymphadenopathy, and who were not candidates for standard-dose fludarabine + cyclophosphamide + rituximab (FCR) therapy.

Subjects must have met all of the following inclusion criteria to have been eligible for participation in this study:

1) Male or female ≥ 18 years of age
2) Diagnosis of B-cell CLL, according to the International Workshop on Chronic Lymphocytic Leukemia and documented within medical records
3) Not a candidate for fludarabine therapy based on either:
    a) creatinine clearance < 70 ml/min, or
    b) CIRS score > 6, by the assessment of the investigator
4) No prior therapy for CLL other than corticosteroids for disease complications
5) CLL that warranted treatment based on any of the following criteria:
    a) Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or
    b) Progressive or symptomatic or massive splenomegaly (ie, lower edge of spleen ≥ 6 cm below the left costal margin), or
    c) Progressive or symptomatic or massive lymphadenopathy (ie, ≥ 10 cm in the longest diameter), or
    d) Progressive lymphocytosis in the absence of infection, with an increase in blood absolute lymphocyte count (ALC) ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/µL), or
    e) Autoimmune anemia and/or thrombocytopenia that was poorly responsive to corticosteroids or other standard therapy, or
    f) Constitutional symptoms, as evidenced by:
        i) Unintentional weight loss of ≥ 10% within the previous 6 months, or
        ii) Significant fatigue (Eastern Cooperative Oncology Group [ECOG] Performance Status of 2: inability to work or perform usual activities), or
        iii) Fevers >100.5 °F or 38.0 °C for ≥ 2 weeks without evidence of infection, or
        iv) Night sweats for > 1 month without evidence of infection
6) Presence of measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measured ≥ 2.0 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by computed tomography [CT] or magnetic resonance imaging [MRI] and confirmed by the Independent Review Committee).
7) ECOG Performance Status of ≤ 2

8) Required baseline laboratory data (within 28 days prior to randomization) as shown in the following table:

Organ System	Parameter	Required Value
Hematopoietic	ANC[a]	$\geq 1 \times 10^9$/L
	Platelets[a]	$\geq 75 \times 10^9$/L
	Hemoglobin[a]	≥ 100 g/L (10.0 g/dL or 6.2 mmol/L)
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 × ULN
	Serum AST	
Renal	C_{Cr}[b]	≥ 30 mL/min
Pregnancy	β-hCG[c]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody, or positive HBc antibody and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody was positive)

Abbreviations: β-hCG = beta human chorionic gonadotropin; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eC_{Cr} = estimated creatinine clearance, HBc antibody = anti-hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, Ig = immunoglobulin, PCR = polymerase chain reaction, ULN = upper limit of normal

a Neutropenia, thrombocytopenia, or anemia of any grade were permitted if abnormality was related to bone marrow involvement with CLL (as documented by bone marrow biopsy/aspirate), or if autoimmune in origin (anemia and thrombocytopenia)

b As calculated by the Cockcroft-Gault formula or measured

c For women of child-bearing potential only; serum β-hCG must have been negative during screening and urine pregnancy test must have been negative at randomization (Visit 2)

9) Female subjects of childbearing potential, willing to use a protocol-recommended method of contraception during heterosexual intercourse from the signing of informed consent up to 30 days from the last dose of IDL or Ch or 18 months from the last dose of Obi, whichever was later

10) Male subjects of reproductive potential engaged in intercourse with females of childbearing potential, and were willing to use a protocol-recommended method of contraception during heterosexual intercourse from the randomization visit up to 3 months from the last dose of IDL or Ch or 18 months from the last dose of Obi (whichever was later); subjects willing to refrain from sperm donation from the randomization visit up to 3 months from the last dose of IDL or Ch or 18 months from the last dose of Obi (whichever was later)

11) Lactating females must have agreed to discontinue nursing before study drug administration.

12) In the judgment of the investigator, participation in the protocol must have offered an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL.

13) Were willing and able to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

14) Evidence of a signed informed consent

Subjects who met any of the following exclusion criteria were not to be enrolled in this study:

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation)
2) Known presence of myelodysplastic syndrome
3) History of a non-CLL malignancy with the following exceptions:
   a) the malignancy had been in remission without treatment for ≥ 5 years prior to randomization, or
   b) carcinoma in situ of the cervix, or
   c) adequately treated basal or squamous cell skin cancer or other localized non-melanoma skin cancer, or
   d) asymptomatic prostate cancer without known metastatic disease, with no current requirement for therapy or requiring only hormonal therapy, and with normal prostate-specific antigen for ≥ 1 year prior to enrollment, or
   e) DCIS of the breast treated with lumpectomy alone, or
   f) Other adequately treated Stage 1 or 2 cancer currently in complete remission
4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for IDL, Obi, or Ch
5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization
6) Ongoing drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver or portal hypertension
7) History of non-infectious pneumonitis
8) Ongoing inflammatory bowel disease
9) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation
10) Ongoing immunosuppressive therapy other than corticosteroids.
11) Received last dose of study drug on another therapeutic clinical trial within 30 days prior to randomization
12) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results
13) Prior major surgery within 30 days before randomization

Duration of Treatment: IDL was taken continuously for up to 96 weeks, and the treatment durations with Obi and/or Ch were 21 and 23 weeks, respectively.

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

Idelalisib: 150-mg or 100-mg tablets were taken orally twice daily in a continuous manner for 96 weeks. The 150-mg tablets were used for initial therapy, and the 100-mg tablets were provided for subjects who required a dose reduction.

Lot numbers administered in this study:

IDL 150 mg: CV1402B1, CV1305B1, NSZV

IDL 100 mg: CV1302C1, NSZS

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

Obinutuzumab: 100 mg intravenously (IV) on Day 1 and 900 mg on Day 2 (Week 0); thereafter 1000 mg on Day 8 (Week 1), Day 15 (Week 2), and on Week 4, 8, 12, 16, and 20 for a total of 8 doses of 1000 mg over 21 weeks; if the 100-mg infusion on Day 1 was well tolerated, the remaining 900 mg, scheduled for Day 2, could be administered on Day 1.

Lot numbers for Obi provided by Gilead and administered to subjects: H0029B05, H0033B03, H0035B12 (Canada only), H0030B08C (Canada only)

Chlorambucil: 0.5 mg/kg orally on Day 1 (Week 0) and every other week (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22) for 12 doses (6 cycles) over 23 weeks; subjects who exhibited significant hematotoxicity to Ch and who would not tolerate 12 doses (6 cycles), as few as 6 doses (3 cycles) could be administered.

Lot numbers for Ch provided by Gilead and administered to subjects: 311239, 411444

Criteria for Evaluation:

In March 2016, an increased rate of deaths and serious adverse events (SAEs) among subjects with early-line iNHL and front-line CLL treated with IDL in combination with standard therapies compared with the control groups was observed by the independent DMC in a pooled analysis of 3 Phase 3 placebo-controlled studies (Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125). Gilead reviewed the unblinded data, and terminated the 3 Phase 3 placebo-controlled studies, in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration. Because the factors contributing to the imbalance in SAEs and deaths were not well understood, the decision was made to terminate the current study as well. A letter to investigators was issued globally on 11 March 2016 providing written notification of the safety findings and decision to terminate the study. The last patient last visit (LPLV) occurred 13 May 2016.

Efficacy: The study was discontinued early, with only 57 enrolled subjects. None of the subjects had reached the prespecified primary efficacy endpoint of disease progression or death, therefore the prespecified efficacy analyses were not conducted.

Pharmacokinetics/Pharmacodynamics: Trough (predose) and peak (1.5-hour samples) plasma concentrations of IDL, and its metabolite, GS-563117, assessed by a validated bioanalytical method. Pharmacodynamic analyses were not conducted.

Safety: The overall safety profile was 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, SAEs, or AEs leading to discontinuation of study treatment.

Statistical Methods:

Data were analyzed and presented for the 3 mutually exclusive treatment groups: the safety run-in IDL + Obi treatment group, the randomized IDL + Obi treatment group, and the randomized Ch + Obi treatment group. In addition, data were analyzed and presented for the combined IDL + Obi treatment group, which comprised subjects in the safety run-in and randomized IDL + Obi treatment groups. Unless otherwise specified, reference to the IDL + Obi treatment group refers to the combined IDL + Obi treatment group.

Efficacy: The study was discontinued early, with only 57 enrolled subjects. None of the subjects had reached the prespecified primary efficacy endpoint of disease progression or death, therefore the prespecified efficacy analyses were not conducted.

Demographic Data and Baseline Characteristics: Subject demographics and baseline disease characteristics are listed by subject. Subject demographic variables (ie, age, sex, race, and ethnicity) were summarized by treatment group using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. Other baseline characteristics were summarized by treatment group using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables.

Demographic and baseline characteristic data were analyzed using the Intent-to-Treat (ITT) Analysis Set, which included all enrolled or randomized subjects regardless of whether subjects were actually treated, or whether subjects received a different treatment regimen to that which they were assigned or randomized.

Safety: Clinical and laboratory AE data focused on treatment-emergent events. Safety data are listed by subject. Treatment-emergent AEs, treatment-related AEs, SAEs, and AEs leading to permanent study drug discontinuation were summarized by treatment group, system organ class (SOC), and preferred term (PT), using the current version of the Medical Dictionary for Regulatory Activities version 19.0. Laboratory results and change from predose values for selected laboratory tests were summarized by treatment group at scheduled visits. The incidence of treatment-emergent laboratory abnormalities was summarized by treatment group.

In the analysis of AEs of interest (AEIs), diarrhea/colitis, pneumonitis, febrile neutropenia, and progressive multifocal leukoencephalopathy (PML) were defined by the respective PTs. Rash and bowel perforation were both defined per Gilead Medical Search Term (MST). Infections ≥ Grade 3 were defined by events within the SOC infections and infestations and by the single PT febrile neutropenia. Cytomegalovirus (CMV) infection was defined by the HLT cytomegaloviral infections, the PT cytomegalovirus test positive, and verbatim terms containing 'CMV' or 'cytomegalo'. *Pneumocystis jirovecii* pneumonia (PJP) was defined by the HLT pneumocystis infections.

Adverse events of interest were summarized similarly to treatment-emergent AEs, by treatment group. Summaries and plots of incidence and prevalence of AEIs by 4-week time intervals are also provided. Time to first onset of AEIs and time to resolution were summarized using Kaplan-Meier curves and estimates.

The exposure-adjusted AE rate was defined as the number of subjects with a specific AE divided by the total exposure-time among subjects in the treatment group at risk of an initial occurrence of the event. Exposure-adjusted rates for AEs and laboratory abnormalities were summarized by treatment group.

Vital signs data were summarized by treatment group.

All safety and exposure data were analyzed using the Safety Analysis Set, which included subjects who received at least 1 dose of study drug, with subjects grouped according to the actual treatment received.

Pharmacokinetics: Plasma concentrations of IDL and its major metabolite GS-563117 are listed. Data were summarized using descriptive statistics. All PK data were analyzed using the Pharmacokinetics (PK) Analysis Set, which included subjects in the Safety Analysis Set who had the necessary baseline and on-study measurements to provide interpretable results for the specific parameter of interest.

Pharmacodynamics: Pharmacodynamic analyses were not conducted.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 57 subjects were in the ITT Analysis Set, including 8 subjects enrolled into the safety run-in and 49 subjects who were randomized (25 to the IDL + Obi group, 24 to the Ch + Obi group). Overall, 1 subject randomized to each treatment group did not receive study drug. Four subjects withdrew consent or were lost to follow up prior to study termination; the remaining 53 subjects discontinued due to early study termination. No subject completed the study per protocol or met the primary endpoint of disease progression or death.

Consistent with the advanced age typical of the general CLL population, most subjects were ≥ 65 years of age, with a median age of 70 years (range, 56 to 89). Across treatment groups, most subjects were male (64.9%) and white (87.7%). Overall, 8.8% of subjects were classified with race “Not Permitted” (ie, not permitted to report). None of the subjects in any treatment group were known to be Hispanic or Latino. Per protocol, all subjects had an ECOG Performance Status of 0, 1, or 2, and approximately 86% of subjects had a Performance Status of 0 or 1. Generally, subjects in the combined IDL + Obi treatment group demonstrated lower ECOG Performance Status at baseline (0: 27.3%, 9 subjects; 1: 57.6%, 19 subjects; 2: 15.2%, 5 subjects) compared with subjects in the Ch + Obi group (0: 58.3%, 14 subjects; 1: 29.2%, 7 subjects; 2: 12.5%, 3 subjects). All other demographic factors were balanced across treatment groups.

Randomization was stratified by central laboratory determination of 17p deletion status (presence versus absence) and IgHV gene mutation status in CLL cells (unmutated versus mutated), as well as by clinical assessment of Rai disease staging (0–II versus III–IV). At randomization, more subjects had advanced disease than earlier-stage disease, as indicated by a higher proportion of subjects who had disease assessed at Rai Stage III to IV (59.6%, 34 subjects). Per central laboratory determination, subjects were more likely to have unmutated IgHV in CLL cells (66.7%, 38 subjects), and 17p deletions in CLL cells were seen at a frequency expected for a treatment-naive population (10.5%, 6 subjects).

The median (Q1, Q3) time since diagnosis of CLL was 33.25 (11.10, 60.35) months, with a range of a few weeks to over 16 years. At diagnosis, Rai Stage was missing for 20 subjects (35.1%). Among the subjects who had available Rai Staging at diagnosis (n=37), few subjects at diagnosis had advanced disease (Rai Stage III–IV: 8/37 subjects, 21.6%); however a higher proportion of subjects at screening had advanced disease (Rai Stage III–IV: 34/57 subjects, 59.6%). Per protocol, subjects must have been ineligible for fludarabine therapy based on either

creatinine clearance < 70 ml/min or a Cumulative Illness Rating Scale (CIRS) score > 6. These requirements were reflected in the greater number of subjects with a total CIRS score > 6 (80.7%, 46 subjects). The median (Q1, Q3) total CIRS score was 8.0 (7.0, 10.0), ranging from 2 to 16. Disease characteristics were balanced across treatment groups, except for a slight imbalance in the proportion of subjects with a total CIRS score > 6 in the IDL + Obi group (87.9%, 29 subjects) compared with the Ch + Obi group (70.8%, 17 subjects).

Efficacy Results: The prespecified efficacy analyses were not conducted.

Pharmacokinetic/Pharmacodynamic Results: Median trough concentrations of IDL and its major metabolite GS-563117 were comparable at predose or 1.5 hours postdose at Week 2, 8, and 20 in the IDL + Obi treatment group. Median trough concentrations of IDL were similar to those observed in other monotherapy studies (eg, Study 101-02) and to estimates from population PK modeling following IDL monotherapy 150 mg twice daily. These results suggest that there was no clinically meaningful change in the PK of IDL or its primary metabolite when IDL or its primary metabolite was coadministered with Obi.

Pharmacodynamic analyses were not conducted.

Safety Results: Among subjects who received IDL + Obi treatment in the safety run-in or randomized phases, the median (Q1, Q3) duration of exposure to IDL was 2.09 (0.79, 3.04) months, with a range of 0.16 to 10.35 months. The median (Q1, Q3) duration of exposure to IDL for subjects enrolled in the initial safety run-in was higher (6.82 [5.80, 7.58] months) than that for subjects subsequently randomized to the IDL + Obi treatment group (1.30 [0.64, 2.29] months).

Key safety findings were as follows:

Adverse Events: Adverse events were common, occurring in 27 subjects (84.4%) in the IDL + Obi treatment group and 21 subjects (91.3%) in the Ch + Obi treatment group. The most commonly reported AEs by treatment group were as follows:

- IDL + Obi: ALT increased, AST increased (37.5%, 12 subjects each), neutropenia (31.3%, 10 subjects), and anemia, diarrhea (25.0%, 8 subjects each)
- Ch + Obi: infusion-related reactions (60.9%, 14 subjects), neutropenia (39.1%, 9 subjects), and nausea, pyrexia (17.4%, 4 subjects each)

Adverse events of any grade that had an exposure-adjusted incidence rate ≥ 0.75 events/subject-year in the IDL + Obi or Ch + Obi treatment groups were as follows:

- IDL + Obi: ALT increased, AST increased (1.74 events/subject-year each), neutropenia (1.52 events/subject-year), anemia (1.00 events/subject-year), diarrhea (0.98 events/subject-year), and infusion-related reactions (0.75 events/subject-year)
- Ch + Obi: infusion-related reactions (7.00 events/subject-year), neutropenia (2.65 events/subject-year), nausea (1.00 events/subject-year), pyrexia (0.95 events/subject-year), and tumor lysis syndrome (TLS; 0.75 events/subject-year)

Adverse events with an exposure-adjusted incidence rate ≥ 0.5 events/subject-year higher in the IDL + Obi treatment group compared with the Ch + Obi treatment group were as follows: ALT increased, AST increased (1.74 vs. 0.22 events/subject-year each) and diarrhea (0.98 vs. 0.21 events/subject-year).

Adverse events with an exposure-adjusted incidence rate ≥ 0.5 events/subject-year higher in the Ch + Obi treatment group compared with the IDL + Obi treatment group were as follows: infusion-related reaction (7.00 vs. 0.75 events/subject-year), neutropenia (2.65 vs. 1.52 events/subject-year), nausea (1.00 vs. 0.47 events/subject-year), pyrexia (0.95 vs. 0.32 events/subject-year), and TLS (0.75 vs. 0.00 events/subject-year).

Adverse Events of Interest: Adverse events of interest were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade PML, any grade pneumonitis, and ≥ Grade 3 rash. Following from safety findings identified in March 2016, the AEI list was expanded to include infection events (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade CMV infection, and any grade PJP).

No subject experienced any grade PML, bowel perforation, PJP, or CMV infection.

Diarrhea/Colitis

Two subjects (6.3%) in the IDL + Obi group and no subject in the Ch + Obi group had ≥ Grade 3 diarrhea and/or colitis. Both subjects who experienced ≥ Grade 3 diarrhea/colitis had worst severity of Grade 3. The PT in both cases was diarrhea. The exposure-adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.20 events/subject-year in the IDL + Obi group. In the IDL + Obi group, no subject had an IDL dose reduction, 1 subject (3.1%) had an interruption in IDL dosing, and no subject discontinued IDL treatment due to ≥ Grade 3 diarrhea and/or colitis. No deaths due to diarrhea and/or colitis were reported.

Pneumonitis

Two subjects (6.3%) in the IDL + Obi group and no subject in the Ch + Obi group had pneumonitis of any grade. The exposure-adjusted incidence rate for pneumonitis was 0.20 events/subject-year in the IDL + Obi group. In the IDL + Obi group, no subject had an IDL dose reduction, 1 subject (3.1%) had an interruption in IDL dosing, and no subject discontinued IDL treatment due to pneumonitis. No deaths due to pneumonitis were reported.

Rash

Two subjects (6.3%) in the IDL + Obi group and no subject in the Ch + Obi group had ≥ Grade 3 rash. The exposure-adjusted incidence rate for ≥ Grade 3 rash was 0.20 events/subject-year in the IDL + Obi group. In the IDL + Obi group, no subject had an IDL dose reduction, 1 subject (3.1%) had an interruption in IDL dosing, and no subject discontinued IDL treatment due to ≥ Grade 3 rash. No deaths due to ≥ Grade 3 rash were reported.

Infections

Seven subjects (21.9%) in the IDL + Obi group and 5 subjects (21.7%) in the Ch + Obi group had ≥ Grade 3 infection. One case in each treatment group was assessed as life-threatening (Grade 4; IDL + Obi: sepsis syndrome; Ch + Obi: herpes zoster). The exposure-adjusted incidence rate for ≥ Grade 3 infection was 0.75 events/subject-year in the IDL + Obi group and 1.28 events/subject-year in the Ch + Obi group. The median (min, max) time to onset of the first ≥ Grade 3 infection event was 1.4 (0.1, 2.9) months in the IDL + Obi group and 0.5 (0.1, 0.7) months in the Ch + Obi group. The median (min, max) time to resolution of any ≥ Grade 3 infection was 0.3 (0.2, 0.4) months in the IDL + Obi group and 0.2 (0.2, 0.4) months in the Ch + Obi group. In the IDL + Obi group, no subject had any IDL dose reductions or interruptions due to ≥ Grade 3 infection, and 1 subject (3.1%) discontinued IDL treatment due to ≥ Grade 3 infection. No deaths due to ≥ Grade 3 infection were reported.

Febrile Neutropenia

Two subjects (6.3%) in the IDL + Obi group and 2 subjects (8.7%) in the Ch + Obi group experienced ≥ Grade 3 febrile neutropenia. The exposure-adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.20 events/subject-year in the IDL + Obi group and 0.44 events/subject-year in the Ch + Obi group. In the IDL + Obi group, no subject had any IDL dose reductions or interruptions, and no subject discontinued IDL treatment due to ≥ Grade 3 febrile neutropenia. No deaths due to ≥ Grade 3 febrile neutropenia were reported.

Deaths: No deaths were reported in any subjects enrolled or randomized into the study.

Serious Adverse Events: Serious adverse events were reported for 14 subjects (43.8%) in the IDL + Obi group, and 8 subjects (34.8%) in the Ch + Obi group. Serious adverse events were consistent with the underlying disease, with events occurring most commonly in the SOC of infections and infestations (4 subjects [12.5%] in the IDL + Obi group and 3 subjects [13.0%] in the Ch + Obi group), followed by blood and lymphatic system disorders (3 subjects [9.4%] in the IDL + Obi group and 2 subjects [8.7%] in the Ch + Obi group).

The most frequently reported SAEs by PT were as follows:

- IDL + Obi: anemia and pneumonitis (6.3%, 2 subjects each)
- Ch + Obi: anemia, febrile neutropenia, sepsis, gastroenteritis, herpes zoster, hypersensitivity, hypertension, pneumonia, pyelonephritis, Richter's syndrome, secondary immunodeficiency, and TLS (4.3%, 1 subject each)

Adverse Events Leading to IDL Dose Modifications: In the IDL + Obi group, 3 subjects (9.4%) discontinued IDL due to an AE (Grade 3 autoimmune colitis, Grade 3 sepsis, and Grade 4 abnormal liver function tests). Overall, 16 subjects (50.0%) in the IDL + Obi group had AEs that led to IDL dose interruption. Elevations in ALT or AST were the most common AEs leading to IDL dose modifications. Elevations in ALT (25.0%, 8 subjects) were all Grade 3 or 4 (4 subjects, 12.5% each) and increases in AST (25.0%, 8 subjects) were Grade 2 (6.3%, 2 subjects) or 3 (18.8%, 6 subjects). The only other AE that led to IDL dose interruption in more than 1 subject was upper respiratory tract infection (6.3%, 2 subjects). One AE led to a reduction in IDL dose: Grade 1 maculopapular rash in 1 subject (3.1%) in the IDL + Obi group.

Clinical Laboratory Evaluations: The most common treatment-emergent hematologic abnormalities of any grade in both the IDL + Obi and Ch + Obi treatment groups were decreased neutrophil count (IDL + Obi: 71.9%, Ch + Obi: 73.9%), decreased white blood cell (IDL + Obi: 65.6%, Ch + Obi: 87.0%), and decreased lymphocyte count (IDL + Obi: 43.8%, Ch + Obi: 69.6%). When adjusted for exposure, the incidence rates of hematologic abnormalities for most parameters were higher in the Ch + Obi treatment group compared with the IDL + Obi treatment group. These cytopenias accounted for all hematologic laboratory abnormalities with an exposure-adjusted incidence ≥ 2 events/subject-year higher in the Ch + Obi treatment group compared with the IDL + Obi treatment group as follows: decreased lymphocyte count (7.89 vs. 1.96 events/subject-year), decreased neutrophil count (7.42 vs. 5.58 events/subject-year), and decreased white blood cell count (16.49 vs. 4.09 events/subject-year).

The most common treatment-emergent serum chemistry abnormality was increased ALT, occurring in 68.8% of subjects in the IDL + Obi group and 30.4% of subjects in the Ch + Obi group. The second most common serum chemistry abnormality was increased AST, occurring in 59.4% of subjects in the IDL + Obi group and 17.4% of subjects in the Ch + Obi group.

The exposure-adjusted incidence rates of most serum chemistry abnormalities (any grade) were generally higher in the IDL + Obi group compared with the Ch + Obi group. Serum chemistry laboratory abnormalities with an adjusted incidence ≥ 0.5 events/subject-year higher in the IDL + Obi treatment group compared with the Ch + Obi treatment group were as follows: increased ALT (5.19 vs. 1.90 events/subject-year), increased AST (3.14 vs. 0.98 events/subject-year), and increased alkaline phosphatase (ALP; 0.89 vs. 0.00 events/subject-year).

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

Laboratory assessment of ALT elevation occurred more commonly in subjects in the IDL + Obi group compared with the Ch + Obi group. Overall, 22 subjects (68.8%) in the IDL + Obi group had treatment-emergent ALT elevations of any grade (11 subjects [34.4%] with ≥ Grade 3 abnormalities), compared with 7 subjects (30.4%) in the Ch + Obi group (1 subject [4.3%] with ≥ Grade 3 abnormalities). For AST elevations, 19 subjects (59.4%) in the IDL + Obi group had treatment-emergent abnormalities of any grade (9 subjects [28.1%] with ≥ Grade 3 abnormalities), compared with 4 subjects (17.4%) in the Ch + Obi group (1 subject [4.3%] with ≥ Grade 3 abnormalities). A total of 11 subjects (34.4%) in the IDL + Obi group had Grade 3 or 4 ALT and/or AST increases, compared with 1 subject (4.3%) in the Ch + Obi group. The exposure-adjusted incidence of ALT increase was 5.19 events/subject-year in the IDL + Obi group and 1.90 events/subject-year in the Ch + Obi group. The exposure-adjusted incidence of AST increase was 3.14 events/subject-year in the IDL + Obi group and 0.98 events/subject-year in the Ch + Obi group.

For the 11 subjects (34.4%) in the IDL + Obi group who experienced Grade 3 or 4 ALT elevations or AST elevations, the median (min, max) time to onset of the first Grade 3 or 4 event was 6.43 (2.6, 16.6) weeks. Transaminase elevations resolved to ≤ Grade 1 with a median (min, max) time of 4.14 (2.1, 6.1) weeks.

One subject in the Ch + Obi group, and no subject in the IDL + Obi group experienced elevation of total bilirubin > 1.5 × ULN; no subject experienced elevations of total bilirubin > 2 × ULN. Fourteen subjects (43.8%) in the IDL + Obi group and 1 subject (4.3%) in the Ch + Obi group experienced elevations of AST or ALT ≥ 3 × ULN, and in half of these subjects in the IDL + Obi group (7 subjects, 21.9%), elevations in AST or ALT were ≥ 20 × ULN. Three subjects (9.4%) in the IDL + Obi group (and none in the Ch + Obi group) experienced elevated (> 1.5 × ULN) ALP. No subject experienced AST or ALT elevations > 3 × ULN concurrent with elevations in total bilirubin > 2 × ULN and ALP ≤ 1.5 × ULN at any time up to 30 days after the last dose of study drug.

Twenty-three subjects (71.9%) in the IDL + Obi group and 17 subjects (73.9%) in the Ch + Obi group experienced treatment-emergent neutropenia. Overall, 8 subjects (25.0%) in the IDL + Obi group and 8 subjects (34.8%) in the Ch + Obi group had decreased neutrophil counts, with a worst grade postbaseline ≥ Grade 3. The exposure-adjusted incidence rate of laboratory abnormalities of any grade neutropenia was 5.58 events/subject-year in the IDL + Obi group and 7.42 events/subject-year in the Ch + Obi group. Median neutrophil counts were generally stable over time in both treatment groups.

CONCLUSIONS: No imbalance in early deaths or incidence of SAEs was observed at the time of study termination. No subject died within 30 days of the last dose of study drug in either treatment group. The incidence of the AEI ≥ Grade 3 infection was comparable in the IDL + Obi (21.9%, 7 subjects) and Ch + Obi (21.7%, 5 subjects) treatment groups. When adjusted for exposure, infection rates were slightly lower in the IDL + Obi group (0.75 events/subject-year) compared with the Ch + Obi group (1.28 events/subject-year). Exposure-adjusted incidence rates of transaminase elevations (ALT or AST) were higher in the IDL + Obi group, and the exposure-adjusted rate for neutropenia was higher in the Ch + Obi group.

The safety conclusions of this study were as follows:

- The most commonly reported AEs in the IDL + Obi group were ALT increased, AST increased (37.5%, 12 subjects each), neutropenia (31.3%, 10 subjects), and anemia, diarrhea (25.0%, 8 subjects each). The most commonly reported AEs in the Ch + Obi group were infusion-related reactions (60.9%, 14 subjects), neutropenia (39.1%, 9 subjects), and nausea, pyrexia (17.4%, 4 subjects each).
- There were no imbalances in deaths or SAEs observed between the IDL+ Obi and Ch + Obi treatment groups, as was observed in the pooled analysis of three other Phase 3 clinical studies in first-line CLL and early-line iNHL (Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125).
- There was no difference in the incidence of the AEI ≥ Grade 3 infection between the treatment groups (IDL + Obi: 7 subjects, 21.9%; Ch + Obi: 5 subjects, 21.7%)
- Overall, 22 subjects (68.8%) in the IDL + Obi group had treatment-emergent elevations in ALT of any grade (11 subjects [34.4%] with ≥ Grade 3 abnormalities), compared with 7 subjects (30.4%) in the Ch + Obi group (1 subject [4.3%] with ≥ Grade 3 abnormalities).
- The incidence of exposure-adjusted transaminase elevations was higher in the IDL + Obi group and the incidence of exposure-adjusted cytopenias was higher in the Ch + Obi group.