FINAL ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas
Name of Test Drug:	Idelalisib (Zydelig®, GS-1101)
Dose and Formulation:	150-mg tablet taken orally twice daily
Indication:	Indolent Non-Hodgkin Lymphomas • Follicular lymphoma • Small lymphocytic lymphoma • Lymphoplasmacytic lymphoma (with or without Waldenström macroglobulinemia) • Marginal zone lymphoma
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Dr. Foster City, CA 94404 USA
Study No.:	GS-US-313-0125
Phase of Development:	Phase 3
IND No.:	101254
EudraCT No.:	2012-004034-42
ClinicalTrials.gov Identifier	NCT01732926
Study Start Date:	02 January 2013 (First Subject Screened)
Study End Date:	17 May 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Gilles Salles, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Brian Koh, MD Telephone: PPD Fax: PPD
Report Date:	30 November 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

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

STUDY SYNOPSIS
Study GS-US-313-0125
Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404
USA

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas

Investigators: Multicenter study

Study Centers: A total of 146 study sites in Australia, Canada, Czech Republic, France, Germany, Israel, Italy, Poland, Russia, South Korea, Spain, Sweden, Taiwan, United Kingdom, United States (US)

Publications: There are no publications at the time of this clinical study report

Study Period:
02 January 2013 (First Subject Screened)
17 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 addition of idelalisib (IDL [GS-1101, Zydelig®]) to bendamustine + rituximab (BR) on progression-free survival (PFS) in subjects with previously treated indolent non-Hodgkin lymphoma (iNHL)

The secondary objectives of this study were as follows:

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

Methodology: GS-US-313-0125 was a Phase 3, multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study in subjects with previously treated recurrent iNHL.

Subjects were allocated 2:1 to IDL + BR (Group A) or placebo + BR (Group B), respectively, via an interactive web response system. Fixed-block centralized randomization allocated subjects within the 8 strata defined by the intersection of 3 binary stratification factors: tumor type (follicular lymphoma [FL] versus others), tumor burden (high versus low as determined by the independent review committee [IRC]), and time since completion of last prior systemic therapy for iNHL (< 18 months versus ≥ 18 months).

Idelalisib or placebo was taken orally, twice daily (continuously). All subjects also received a maximum of 6 infusions of rituximab and 8 to 12 infusions of bendamustine.

All subjects received rituximab with a planned dosing regimen of 375 mg/m^2 administered intravenously on Day 1 in the first cycle, and on Day 1 of each of the 5 subsequent 4-week cycles, for a total of 6 cycles. All subjects were also administered bendamustine intravenously at a starting dose of 90 mg/m^2/infusion on Days 1 and 2 of each of the 4 to 6 planned, 4-week treatment cycles. At the discretion of the investigator, and based on prior treatment with bendamustine and tolerability, the subject received a minimum of 4 cycles and up to a maximum of 6 cycles of bendamustine.

Early Study Termination: In March 2016, this study was terminated early based on an aggregate safety signal. An increased risk of death and higher incidence of serious adverse events (SAEs) was observed among subjects receiving IDL in combination with standard therapies compared with the control groups in a pooled analysis conducted by the independent Data Monitoring Committee (DMC) during regular review of three Phase 3 placebo-controlled clinical studies in first-line chronic lymphocytic leukemia (CLL) and early-line iNHL (Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125). Gilead Sciences, Inc. (Gilead) reviewed the unblinded data and terminated this study in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration (FDA). A letter was sent to all participating investigators on 11 March 2016, advising them of the safety findings and of the decision to terminate the study. The last patient last visit (LPLV) occurred 17 May 2016.

Number of Subjects (Planned and Analyzed):

Planned:	Approximately 450 subjects, 300 subjects in the IDL + BR group and 150 subjects in the placebo + BR group
Enrolled:	475 subjects, 320 in the IDL + BR group and 155 in the placebo + BR group
Analyzed:	472 subjects total, 317 in the IDL + BR group and 155 in the placebo + BR group (Safety Analysis Set)

Diagnosis and Main Criteria for Inclusion: The target population consisted of subjects ≥ 18 years of age with previously treated recurrent iNHL, including FL (Grade 1, 2, or 3a), small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL) (splenic, nodal, or extranodal), or lymphoplasmacytic lymphoma (LPL) (with or without Waldenström macroglobulinemia [WM]) who had measurable lymphadenopathy, had received prior anti-CD20 antibody-containing chemotherapy, and who had disease that was not refractory to bendamustine.

Duration of Treatment: Idelalisib/placebo was taken continuously. All subjects also received a maximum of 6 infusions of rituximab and 8 to 12 infusions of bendamustine. The study was initially planned to continue until approximately the 267th PFS event occurred.

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

150 mg IDL or matching placebo was taken orally twice daily starting on Day 1 and administered continuously thereafter; subjects who required a dose reduction received IDL 100-mg tablets or matching placebo.

IDL Lot Numbers

150 mg: CY1202B1; CV1110D2; CV1204B1; CV1206B1; CV1302D1; CV1303B1; CV1401B1

100 mg: CV1110C2; CV1107B1; CY1201B1; CV1304C1; CV1404D1

Placebo Lot Numbers

150 mg: CV1108D1; CV1203B1; CV1408B1

100 mg: CV1109B1; CV1407B1

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

Rituximab: 375 mg/m^2 intravenously on Day 1 of each 28-day cycle of treatment, for up to 6 infusions, as tolerated

Bendamustine: 90 mg/m^2/dose intravenously on Day 1 and Day 2 of each 28-day cycle of treatment for up to 4 to 6 cycles (8 to 12 infusions), as tolerated

Commercial product was used.

Criteria for Evaluation:

Efficacy: Due to the early study termination, the prespecified efficacy analyses were not conducted. An analysis of investigator-assessed PFS (defined as the interval from randomization to the earlier of the first documentation of definitive iNHL disease progression [based on standard criteria] or death from any cause) and OS (defined as the interval from randomization to death from any cause) was conducted using the data that supported the DMC's safety analysis (data cutoff date 15 January 2016). This unplanned analysis (with 100 PFS events, ie, definitive iNHL progression or death) occurred approximately 4 months prior to the planned interim analysis (134 PFS events).

Pharmacokinetics/Pharmacodynamics: Blood samples for pharmacokinetic (PK) analysis of IDL were collected from subjects in the IDL + BR group at predose and at 1.5 hours after IDL dose administration at Weeks 0, 4, 8, and 12. Blood samples for assessments of biomarkers were obtained from all subjects at Weeks 0, 4, 8, 12, 16, 20, 24, and 36 and at 12-week intervals thereafter until the end of study.

Safety: The overall safety profile of each regimen 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, and AEs leading to discontinuation of study drug.

Statistical Methods:

Efficacy: Investigator-assessed PFS and OS were summarized by treatment group.

Pharmacokinetics/Pharmacodynamics: For the IDL + BR group, the plasma concentrations of IDL and its primary metabolite (GS-563117) immediately predose and at 1.5 hours postdose at each relevant clinic visit were summarized using descriptive statistics. No pharmacodynamics or biomarker analyses were done for this report.

Safety: Summaries of AEs focused on treatment-emergent AEs (TEAEs). A TEAE was defined as an event that met 1 or both of the following criteria: (1) any AE with an onset date on or after the study drug start date and no later than 30 days after the permanent discontinuation of study drug, (2) any AE leading to premature discontinuation of study drug. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. The severity of AEs was graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, whenever possible.

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

Laboratory data collected during the study was analyzed and summarized using both quantitative and qualitative methods. Treatment-emergent laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. The number and percentage of subjects with treatment-emergent laboratory abnormalities was provided by laboratory test and treatment group; subjects were categorized according to the most severe postbaseline abnormality grade for a given laboratory test.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: This study was fully enrolled at the time it was terminated for safety reasons. A total of 475 subjects were randomized in a 2:1 ratio (320 to the IDL + BR group, 155 to the placebo + BR group), and were included in the intent-to-treat (ITT) Analysis Set. Of the randomized subjects, 317 in the IDL + BR group and all 155 subjects in the placebo + BR group received treatment, and were included in the Safety Analysis Set.

The investigators assessed that the primary study endpoint of progressive disease or death had been met by 13.1% (62 subjects) of the total study population, including 6.9% (22 subjects) of the IDL + BR group and 25.8% (40 subjects) of the placebo + BR group. Further, 92.2% (295 subjects) of the IDL + BR group and 74.2% (115 subjects) of the placebo + BR group discontinued treatment (ie, IDL/placebo) due to other reasons. Overall, 35.4% (168 subjects) discontinued study treatment due to study termination by the sponsor (29.7% [95 subjects] of the IDL + BR group and 47.1% [73 subjects] of the placebo + BR group). The most common other reasons for discontinuation of IDL/placebo included AEs (39.7% [127 subjects] of the IDL + BR group and 12.3% [19 subjects] of the placebo + BR group), physician decision (10.0% [32 subjects] of the IDL + BR group and 7.1% [11 subjects] of the placebo + BR group), withdrawal by subject (10.6% [34 subjects] of the IDL + BR group and 5.2% [8 subjects] of the placebo + BR group).

Overall, the demographic and baseline characteristics (age, sex, race, body mass index [BMI]) were generally comparable between the 2 treatment groups. The median (first quartile, third quartile [Q1, Q3]) age was 63 (54, 69) years with an age range of 32 to 92 years; 211 subjects (44.4%) were ≥ 65 years of age. A total of 285 subjects (60.0%) were male; the majority subjects were white (77.7%) and the majority of subjects identified as not Hispanic or Latino (82.3%). At study entry, 55.4% of subjects had a Karnofsky performance status (KPS) score of 80 or 90 and 9.9% had a KPS score of 60 or 70.

The iNHL disease characteristics were generally balanced between treatment groups. Prior to study entry, the subject population had presented with iNHL for a median (Q1, Q3) of 5.4 (2.9, 8.7) years, with a range of 0.3 to 34.7 years. Approximately two-thirds of the subjects had FL (62.9%) and the remaining had other subtypes of iNHL, including SLL (11.4%), MZL (14.7%), and LPL/WM (10.9%). The majority of subjects (85.5%) had baseline Ann Arbor Stage of III or IV. Subject distribution by stratification factors (tumor type, tumor burden, and time since completion of last prior systemic therapy for iNHL) was balanced between the 2 treatment groups.

The median (Q1, Q3) number of prior iNHL regimens was 1.0 (1.0, 2.0), with a range of 1 to 11 for subjects in the IDL + BR group and 2.0 (1.0, 3.0), with a range of 1 to 9 for subjects in the placebo + BR group. The median (Q1, Q3) time since last prior regimen was 20.3 (6.5, 42.5) months for subjects in the IDL + BR group and 21.2 (7.6, 37.7) months for subjects in the placebo + BR group.

Efficacy Results: An analysis of investigator-assessed PFS and OS was conducted using the data that supported the DMC's safety analysis (data cutoff date 15 January 2016). The median investigator-assessed PFS was not reached in either the IDL + BR group or the placebo + BR group; the adjusted hazard ratio (HR [95% CI]) was 0.74 (0.50, 1.10).

The median OS was not reached in either the IDL + BR group or placebo + BR group; the adjusted HR (95% CI) was 1.51 (0.71, 3.23).

Pharmacokinetics Results: In general, the plasma concentrations of IDL and GS-563117 appeared to be at steady state by Week 4. The plasma concentrations of IDL and its primary metabolite (GS-563117) at predose and at 1.5 hours postdose were comparable between Week 4 and Week 12. In addition, mean peak and trough concentrations of IDL were comparable with those observed in other monotherapy studies (eg, Study 101-02) and with the population PK modeling estimates following monotherapy with IDL 150 mg twice daily. These data suggest that there is no notable change in the PK profile of IDL when coadministered with BR.

Safety Results: In the Safety Analysis Set, the median (Q1, Q3) duration of exposure to IDL in the IDL + BR group was 6.5 (2.1, 14.9) months, with a range of 0.1 to 34.2 months. The median (Q1, Q3) duration of exposure to placebo in the placebo + BR group was 13.8 (9.0, 18.8) months, with a range of 0.2 to 31.3 months.

The median (Q1, Q3) duration of exposure to bendamustine was 4.7 (2.2, 5.1) months in the IDL + BR group and 4.7 (4.6, 4.8) months in the placebo + BR group.

The median (Q1, Q3) duration of exposure to rituximab was 4.6 (2.8, 5.2) months in the IDL + BR group and 4.6 (4.6, 4.8) months in the placebo + BR group.

The key safety findings were as follows:

Adverse Events: The percentage of subjects who experienced at least 1 AE during the study was similar in both treatment groups (100.0% [317 subjects] in the IDL + BR group and 98.1% [152 subjects] in the placebo + BR group). The most commonly reported AEs by PT in each treatment group were as follows:

- IDL + BR: pyrexia (53.6%, 170 subjects), nausea (50.8%, 161 subjects), and diarrhea (50.8%, 161 subjects)
- Placebo + BR: nausea (41.9%, 65 subjects), neutropenia (34.8%, 54 subjects), and fatigue (32.9%, 51 subjects)

Adverse Events of Interest: The AEI for IDL included any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade progressive multifocal leukoencephalopathy (PML), any grade pneumonitis, and ≥ Grade 3 rash by medical search term (MST). Following from the safety findings identified in March 2016, the AEI list was expanded to include additional infection terms (specifically, ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade cytomegalovirus [CMV] infection, any grade *Pneumocystis jirovecii* pneumonia [PJP]).

The incidence and prevalence of AEI was generally highest during the first 6 to 12 months after treatment initiation, and declined over the duration of the study. No events of bowel perforation or PML of any grade were reported in either treatment group during this study through approximately 39 months of follow-up.

≥ Grade 3 Diarrhea and/or Colitis

For the AEI of diarrhea and/or colitis, the analysis utilized the combined PTs of diarrhea and colitis. In this study, 12.6% (40 subjects) of the IDL + BR group and no subject in the placebo + BR group had ≥ Grade 3 diarrhea and/or colitis. The exposure-adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.15 events/subject-year in the IDL + BR group versus no event in the placebo + BR group. In the IDL + BR group, the median time to onset of the first ≥ Grade 3 event of diarrhea/colitis (n = 40) was 15.6 weeks (range: 0.7 to 81.4 weeks), and the median time to resolution of any ≥ Grade 3 diarrhea/colitis (n = 38) was 1.5 weeks (range: 0.3 to 34.1 weeks). In the IDL + BR group, 3.2% (10 subjects) discontinued the study drug (IDL) due to ≥ Grade 3 diarrhea and/or colitis.

No deaths due to diarrhea and/or colitis were reported in this study.

Any Grade Pneumonitis

For the AEI of pneumonitis, the analysis utilized the single PT of pneumonitis. In this study, 7.9% (25 subjects) of the IDL + BR group and 1.3% (2 subjects) of the placebo + BR group had pneumonitis of any grade; 4.4% (14 subjects) of the IDL + BR group and no subject in the placebo + BR group experienced ≥ Grade 3 pneumonitis. The exposure-adjusted incidence rate for pneumonitis was 0.09 events/subject-year in the IDL + BR group versus 0.01 events/subject-year in the placebo + BR group. In the IDL + BR group, the median time to onset of the first pneumonitis event of any grade (n = 25) was 16.1 weeks (range: 3.0 to 97.1 weeks), and the median time to resolution of any pneumonitis event (n = 21) was 4.6 weeks (range: 0.7 to 34.3 weeks). In the placebo + BR group, the median time to onset of the first pneumonitis event of any grade (n = 2) was 31.4 weeks (range: 19.4 to 43.4 weeks), and the median time to resolution of any pneumonitis event (n = 2) was 6.1 weeks (range: 4.1 to 8.1 weeks).

Overall, 4.4% (14 subjects) in the IDL + BR group and 0.6% (1 subject) in the placebo + BR group discontinued the study drug (IDL/placebo) due to pneumonitis.

One subject in the IDL + BR group (0.3%) died due to a pneumonitis event.

≥ Grade 3 Rash by MST

Rash was defined per Gilead MST. In this study, 18.6% (59 subjects) of the IDL + BR group and 1.3% (2 subjects) of the placebo + BR group had ≥ Grade 3 rash.

The exposure-adjusted incidence rate for ≥ Grade 3 rash was 0.25 events/subject-year in the IDL + BR group versus 0.01 events/subject-year in the placebo + BR group. In the IDL + BR group, the median time to onset of the first ≥ Grade 3 rash event (n = 59) was 2.0 weeks (range: 0.3 to 40.7 weeks), and the median time to resolution of any ≥ Grade 3 rash event (n = 57) was 1.3 weeks (range: 0.1 to 9.6 weeks). In the placebo + BR group, the median time to onset of the first ≥ Grade 3 rash event (n = 2) was 19.9 weeks (range: 17.1 to 22.7 weeks), and the median time to resolution of any ≥ Grade 3 rash event (n = 2) was 1.8 weeks (range: 0.3 to 3.3 weeks).

Overall, 2.8% (9 subjects) in the IDL + BR group and no subject in the placebo + BR group discontinued the study drug (IDL/placebo) due to ≥ Grade 3 rash.

In the IDL + BR group, an SAE of toxic epidermal necrolysis was reported for 1 subject (0.3%),

and an SAE of Stevens-Johnson syndrome was reported for another subject (0.3%). While neither event was reported as fatal, the subject with TEN was noted to undergo progression of both cutaneous and eventual extracutaneous manifestations, leading to the subject's death from bronchiolitis; the subject with SJS recovered.

No deaths specifically due to rash were reported in this study.

≥ Grade 3 Infection

For the AEI of ≥ Grade 3 infection, the analysis utilized the entire SOC of infections and infestations and the additional PT of febrile neutropenia. In this study, 40.1% (127 subjects) of the IDL + BR group and 19.4% (30 subjects) of the placebo + BR group had ≥ Grade 3 infections. The exposure-adjusted incidence rate for ≥ Grade 3 infection was 0.63 events/subject-year in the IDL + BR group versus 0.17 events/subject-year in the placebo + BR group. In the IDL + BR group, the median time to onset of the first ≥ Grade 3 event of infection (n = 127) was 9.4 weeks (range: 0.1 to 115.3 weeks), and the median time to resolution of any ≥ Grade 3 infection (n = 118) was 1.1 weeks (range: 0.1 to 9.9 weeks). In the placebo + BR group, the median time to onset of the first ≥ Grade 3 event of infection (n = 30) was 17.3 weeks (range: 0.1, 100.0 weeks), and the median time to resolution of any ≥ Grade 3 infection (n = 28) was 1.4 weeks (range: 0.3 to 11.0 weeks).

Overall, 6.3% (20 subjects) in the IDL + BR group and 3.2% (5 subjects) in the placebo + BR group discontinued the study drug (IDL/placebo) due to ≥ Grade 3 infection.

The AEI of ≥ Grade 3 infection occurred concomitantly with a ≥ Grade 3 laboratory abnormality of neutropenia (ie, neutropenia occurred within ± 2 weeks of the onset of infection) for 6.6% (21 subjects) of the IDL + BR group and 2.6% (4 subjects) of the placebo + BR group.

A total of 7 subjects (2.2%) in the IDL + BR group and 2 subjects (1.3%) in the placebo + BR group died due to treatment-emergent infections.

≥ Grade 3 Febrile Neutropenia

For the AEI of febrile neutropenia, the analysis utilized the single PT of febrile neutropenia. Overall, 15.1% (48 subjects) of the IDL + BR group and 5.2% (8 subjects) of the placebo + BR group experienced ≥ Grade 3 febrile neutropenia in this study. The exposure-adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.19 events/subject-year in the IDL + BR group versus 0.04 events/subject-year in the placebo + BR group. In the IDL + BR group, the median time to onset of the first ≥ Grade 3 event of febrile neutropenia (n = 48) was 9.9 weeks (range: 0.3 to 85.1 weeks), and the median time to resolution of any ≥ Grade 3 febrile neutropenia (n = 48) was 1.1 weeks (range: 0.1 to 3.9 weeks). In the placebo + BR group, the median time to onset of the first ≥ Grade 3 event of febrile neutropenia (n = 8) was 14.6 weeks (range: 0.6 to 50.3 weeks), and the median time to resolution of any ≥ Grade 3 febrile neutropenia (n = 8) was 1.4 weeks (range: 0.3 to 4.4 weeks).

Overall, 2.2% (7 subjects) in the IDL + BR group and 0.6% (1 subject) in the placebo + BR group discontinued the study drug (IDL/placebo) due to ≥ Grade 3 febrile neutropenia.

One subject in the IDL + BR group (0.3%) died due to a febrile neutropenia event.

Any Grade CMV Infection

For the AEI of CMV infection, the search utilized the entire high-level term (HLT) of

cytomegaloviral infections and the PT of cytomegalovirus test positive. In this study, 4.7% (15 subjects) of the IDL + BR group and no subject in the placebo + BR group had CMV infection of any grade; 2.8% (9 subjects) of the IDL + BR group had ≥ Grade 3 CMV infection.

The exposure-adjusted incidence rate for CMV infection was 0.05 events/subject-year in the IDL + BR group versus no event in the placebo + BR group. In the IDL + BR group, the median time to onset of the first CMV infection event of any grade (n = 15) was 7.6 weeks (range: 3.0 to 79.1 weeks), and the median time to resolution of any CMV infection event (n = 10) was 3.4 weeks (range: 1.3 to 7.6 weeks). In the IDL + BR group, 0.6% (2 subjects) discontinued the study drug (IDL) due to CMV infection.

No deaths due to CMV infection were reported in this study.

Any Grade PJP

For the AEI of PJP, the analysis utilized the entire HLT of *Pneumocystis* infections. In this study, 3.2% (10 subjects) of the IDL + BR group and no subject in the placebo + BR group had PJP of any grade; all events of PJP were ≥ Grade 3.

Of the 173 subjects in the IDL + BR group who did not receive PJP prophylaxis, 1.2% (2 subjects) experienced PJP. Of the 144 subjects who received PJP prophylaxis (at any point during the study), 5.6% (8 subjects) experienced PJP.

The exposure-adjusted incidence rate for PJP was 0.04 events/subject-year in the IDL + BR group versus no event in the placebo + BR group. In the IDL + BR group, the median time to onset of the first PJP event of any grade (n = 10) was 13.3 weeks (range: 8.0 to 62.0 weeks), and the median time to resolution of any PJP event (n = 8) was 3.1 weeks (range: 0.4 to 6.0 weeks). In the IDL + BR group, 1.3% (4 subjects) discontinued the study drug (IDL) due to PJP.

One subject (0.3%) in the IDL + BR group died due to a PJP event; this subject did not receive PJP prophylaxis prior to PJP onset.

Deaths: In the IDL + BR group, 31 subjects (9.8%) died: 24 subjects (7.6%) on study (ie, between randomization and within 30 days from the end of study) and 7 subjects (2.2%) during long-term follow-up. In the placebo + BR group, 13 subjects (8.4%) died: 6 subjects (3.9%) on study and 7 subjects (4.5%) during long-term follow-up. The most common TEAEs that led to death in the IDL + BR group were respiratory failure (1.3%, 4 subjects), septic shock (0.6%, 2 subjects), and pneumonia (0.6%, 2 subjects). In the placebo + BR group, the TEAEs that led to death were reported for 1 subject (0.6%) each and included the following: cardiorespiratory arrest, septic shock (causative organism not specified), encephalitis (causative organism not specified), road traffic accident, and internal hemorrhage (etiology not specified).

Serious Adverse Events: There was an imbalance between the IDL + BR and placebo + BR groups in the percentage of subjects who had SAEs (72.2% versus 37.4%, respectively). The SAEs were generally typical of the population with previously treated, recurrent iNHL and events occurred most commonly in the SOCs of infections and infestations (reported for 31.5% and 15.5% of subjects in the IDL + BR and placebo + BR groups, respectively) and blood and lymphatic system disorders (reported for 19.2% and 8.4% of subjects in the IDL + BR and placebo + BR groups, respectively).

The most frequently reported SAEs by PT were as follows:

- IDL + BR group: pyrexia (21.1%, 67 subjects), febrile neutropenia (14.2%, 45 subjects), and pneumonia (7.6%, 24 subjects)
- Placebo + BR: febrile neutropenia (4.5%, 7 subjects), pneumonia (2.6%, 4 subjects), and anemia (2.6%, 4 subjects)

Within the SOC of infections and infestations, the most frequently reported SAEs by PT were pneumonia (reported for 7.6% [24 subjects] and 2.6% [4 subjects] in the IDL + BR and placebo + BR groups, respectively), sepsis (reported for 2.8% [9 subjects] and 0.6% [1 subject] in the IDL + BR and placebo + BR groups, respectively) and PJP (reported for 2.8% [9 subjects] and no subject in the IDL + BR and placebo + BR groups, respectively).

Deaths due to treatment-emergent infections were reported for 7 subjects (2.2%) in the IDL + BR group (septic shock and pneumonia [2 subjects each] and lung infection, PJP, and sepsis [1 subject each]) and 2 subjects (1.3%) in the placebo + BR group (septic shock and encephalitis [1 subject each]). In addition, 1 subject in the IDL + BR group died due to febrile neutropenia.

Adverse Events Leading to Discontinuation of Study Drug: Overall, AEs that led to study drug discontinuation were reported for a greater percentage of subjects in the IDL + BR group than in the placebo + BR group (45.7% [145 subjects] versus 14.2% [22 subjects], respectively). In the IDL + BR group, AEs that led to study drug discontinuation in ≥ 2% of subjects included the following: diarrhea (5.4%, 17 subjects), pneumonitis (4.4%, 14 subjects), alanine aminotransferase (ALT) increased and rash (each in 3.2%, 10 subjects), neutropenia (2.5%, 8 subjects), and febrile neutropenia and aspartate aminotransferase (AST) increased (each in 2.2%, 7 subjects). In the placebo + BR group, no event that led to study drug discontinuation was reported for ≥ 2% of subjects.

Laboratory Evaluations of Interest: Laboratory evaluations of interest for IDL include reduced neutrophil counts and transaminase elevations, both of which have been commonly reported in prior studies with IDL. Median absolute neutrophil counts (ANC) generally decreased in both treatment groups at early time points from baseline through Week 14 and then remained stable or improved close to baseline levels over time in the total population in both treatment groups. In this study, 61.8% (196 subjects) of the IDL + BR group and 61.3% (95 subjects) of the placebo + BR group had treatment-emergent neutropenia of any grade. Treatment-emergent neutropenia of ≥ Grade 3 occurred in 41.0% (130 subjects) and 36.8% (57 subjects) of the IDL + BR and placebo + BR groups, respectively.

In this study, treatment-emergent elevations (all grades, per laboratory assessments) in serum ALT occurred in 70.0% (222 subjects) of the IDL + BR group (≥ Grade 3 observed in 27.1% [86 subjects]) compared with 24.5% (38 subjects) of the placebo + BR group (≥ Grade 3 observed in 0.6% [1 subject]). Treatment-emergent elevations in serum AST occurred in 61.8% (196 subjects) of the IDL + BR group (≥ Grade 3 observed in 16.4% [52 subjects]) compared with 27.7% (43 subjects) of the placebo + BR group (≥ Grade 3 observed in 0.6% [1 subject]). The Grade 3 or 4 elevations in ALT or AST typically occurred within the first 3 months of therapy (median time to onset 6.1 weeks) and most observed Grade 3 or 4 elevations in ALT or AST for almost all subjects (94.3% [83 of 88 subjects]) resolved to ≤ Grade 1 by the end of the study.

Other Clinical Laboratory Evaluations: Hemoglobin concentrations and platelet counts remained generally stable over time in both the IDL + BR and placebo + BR treatment groups. The exposure-adjusted incidence rates (all grades) of low hemoglobin levels and low counts of leukocytes, lymphocytes, and neutrophils (ANC and segmented neutrophils) were higher in the IDL + BR group than in the placebo + BR group. The exposure-adjusted incidence rates (all grades) were notably higher in the IDL + BR group than in the placebo + BR group for elevations in ALT (2.07 versus 0.24 events/subject-year, respectively), AST (1.49 versus 0.28 events/subject-year, respectively), and gamma-glutamyltransferase (GGT) (1.12 versus 0.32 events/subject-year, respectively).

CONCLUSIONS:

This study was terminated early based on an aggregate safety signal. At the time of the safety findings, an analysis of investigator-assessed PFS and OS was conducted in order to assess the potential benefit versus risk of continued treatment in both groups. In this early-line iNHL population, the risk of continued treatment with IDL in combination with BR was determined to outweigh the potential benefit. Of note, the evaluation of benefit:risk balance in this study was performed at an early point, when the imbalance in SAEs and deaths was first noted and before any potential positive impact of IDL on progression of underlying disease may have been expected to emerge. Because the factors contributing to the SAEs and deaths were not completely understood, the decision was made to terminate this study. Due to the early study termination, the prespecified efficacy analyses were not conducted.

The conclusions from this study are as follows:

- There was an imbalance between the IDL + BR and placebo + BR groups in the percentage of subjects who had SAEs, particularly events in the SOC of infections and infestations (31.5% and 15.5%, respectively).
- The occurrence of AEI related to infections was higher in the IDL + BR group than in the placebo + BR group: ≥ Grade 3 infection (40.1% versus 19.4%, respectively), ≥ Grade 3 febrile neutropenia (15.1% versus 5.2%, respectively), any grade CMV infection (4.7% versus 0.0%, respectively), and any grade PJP (3.2% versus 0.0%, respectively).
- Twenty subjects (6.3%) in the IDL + BR group and 5 subjects (3.2%) in the placebo + BR group experienced TEAEs that led to death. Deaths due to infections were reported for 7 subjects (2.2%) in the IDL + BR group (septic shock and pneumonia [2 subjects each] and lung infection, PJP, and sepsis [1 subject each]) and 2 subjects (1.3%) in the placebo + BR group (septic shock and encephalitis [1 subject each]). In addition, 1 subject in the IDL + BR group died due to febrile neutropenia.