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 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-313-0124
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	101254 2012-004013-13
ClinicalTrials.gov Identifier:	NCT01732913
Study Start Date:	16 January 2013 (First Subject Screened)
Study End Date:	18 May 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Gilles Salles, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Siddhartha Mitra, MD Telephone: PPD Fax: PPD
Report Date:	02 December 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-313-0124
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 Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas

Investigators: Multicenter

Study Centers: A total of 108 sites in Australia, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Poland, Portugal, Romania, Russia, South Korea, Singapore, Spain, Sweden, Taiwan, United Kingdom, and the United States (US).

Publications: Not applicable.

Study Period:

16 January 2013 (First Subject Screened)
18 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) to rituximab (R) 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 rituximab on the onset, magnitude, and duration of tumor control
- To assess the effect of the addition of IDL to rituximab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status
- To assess the effects of the addition of IDL to rituximab on disease-associated biomarkers
- To characterize the effect of rituximab on IDL exposure through evaluation of IDL plasma concentrations over time
- To describe the safety profile observed with the addition of IDL to rituximab
- To estimate health resource utilization associated with the addition of IDL to rituximab

Methodology: GS-US-313-0124 was a Phase 3, multicenter, 2-group, randomized, double-blind, placebo-controlled, parallel-group study in subjects with previously treated recurrent iNHL.

Subjects were allocated 2:1 to Group A (IDL + rituximab) and Group B (placebo + rituximab), respectively, via an interactive web response system (IWRS). 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/placebo was taken orally, twice daily (continuously). Following IRC-confirmed disease progression, subjects randomized to placebo were given the opportunity to receive open-label IDL after they discontinued placebo treatment.

All subjects also received 8 rituximab infusions. Rituximab was administered intravenously in the clinic at a dose of 375 mg/m^2 Weeks 1, 2, 3, 4, 12, 20, 28, and 36. Rituximab was administered until the earliest of subject withdrawal from study, definitive progression of iNHL, intolerable rituximab-related toxicity, pregnancy, initiation of another anti-cancer or experimental therapy, substantial noncompliance with study procedures, study discontinuation, or a maximum of 8 infusions.

Early Study Termination: In March 2016, this study was terminated early based on an aggregate safety signal. An increased rate of deaths and 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 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 safety 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 visit (LPLV) for Study GS-US-313-0124 occurred on 18 May 2016

Number of Subjects (Planned and Analyzed):

Planned:	Approximately 375 subjects, 250 subjects in the IDL + R group and 125 subjects in the placebo + R group
Enrolled:	295 subjects, 198 in the IDL + R group and 97 in the placebo + R group
Analyzed:	295 subjects, 198 in the IDL + R group and 95 in the placebo + R group (Safety Analysis Set)

Diagnosis and Main Criteria for Inclusion: The target population was composed of adult subjects with previously treated recurrent iNHL including FL (Grade 1, 2, or 3a), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL) or Waldenstrom macroglobulinemia (WM), or marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal) who had measurable lymphadenopathy, had received prior anti-CD20-antibody-containing therapy, and who had disease that was not refractory to rituximab.

Duration of Treatment: Idelalisib/placebo was taken continuously. Rituximab was administered up to a maximum of 8 infusions. Upon IRC-confirmed disease progression the investigator and subjects were unblinded. Subjects randomized to Group B (placebo + rituximab) were offered the opportunity to receive open-label IDL 150 mg twice daily as monotherapy. In the open-label extension, IDL was taken continuously. Subjects were to be followed annually for 5 years after study treatment discontinuation.

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

150 mg IDL or placebo to match taken orally twice daily starting on Day 1 and administered continuously thereafter.

IDL Lot Numbers:

150 mg – CY1202B1, CV1206B1, CV1302D1, CV1303B1, CV1308B1, CV1401B1, PCZD, CV1409D1, CV1401B1R

100 mg - CY1201B1, CV1304C1, CV1404D1, CV1304D1, PCZX, CV1404D1, NSZP

Placebo Lot Numbers:

150 mg – CV1108D1, CV1203B1, CV1306B1, CV1408B1

100 mg - CV1109B1, CV1307B1, CV1407B1

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

Rituximab 375 mg/m^2/infusion administered intravenously starting on Day 1 for a total of 8 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 61 PFS events, ie, definitive iNHL progression or death) occurred prior to the planned interim analysis (123 PFS events).

Pharmacokinetics/Pharmacodynamics: Blood samples for pharmacokinetic (PK) analysis of IDL were collected from subjects in the IDL + R group at predose and at 1.5 hours after IDL dose administration at Weeks 0, 2, 8, and 20. Blood samples for assessments of drug activity and potential mechanisms of resistance were obtained prior to therapy on Weeks 0, 2, 8, 36, 48, 72, 96, at MRD assessment visit (if different than Week 36), and at disease progression. Specimens were collected from all subjects.

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; or AEs leading to discontinuation of study drug.

Statistical Methods:

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

Pharmacokinetics/Pharmacodynamics: For IDL + R 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- and rituximab-related AEs; SAEs; IDL/placebo- and rituximab-related SAEs; AEs leading to IDL/placebo and rituximab interruption, AEs leading to IDL/placebo reduction; AEs leading to IDL/placebo and rituximab discontinuation; AEs leading to death; AEs of interest (AEIs) incidence/prevalence 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 lab test and treatment group; subjects were categorized according to the most severe postbaseline abnormality grade for a given lab test.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: At the time the study was terminated for safety reasons, a total of 295 subjects had been randomized in a 2:1 ratio (198 to the IDL + R group, 97 to the placebo + R group) and included in the Intent-to-Treat (ITT) Analysis Set. Of the randomized subjects, all subjects in the IDL +R group and 95 subjects in the placebo + R group received treatment and were included in the Safety Analysis Set.

The investigator assessed that the primary endpoint of progressive disease (PD) or death had been met by 15.9% (47 subjects) of the total population, including 10.6% (21 subjects) of the IDL + R group and 26.8% (26 subjects) of the placebo + R group. Further, 89.4% (177 subjects) of the IDL + R group and 71.1% (69 subjects) of the placebo + R group discontinued treatment (ie, IDL/placebo) due to other reasons. Overall, 42.4% (124 subjects) discontinued study treatment due to study termination by the sponsor (35.9% [71 subjects] of the IDL + R group and 55.7% [54 subjects] of the placebo + R group). The most common other reasons for discontinuation of IDL/placebo included AEs (42.4% [84 subjects] of the IDL + R group and

7.2% [7 subjects] of the placebo + R group), withdrawal by subject (6.6% [13 subjects] of the IDL + R group and 1% [1 subject] of the placebo + R group) and physician decision (3.0% [6 subjects] of the IDL + R group and 5.2% [5 subjects] of the placebo + R group).

Overall, demographics and baseline characteristics (age, sex, race, body mass index [BMI]) were generally comparable between the 2 treatment groups. The median (Q1, Q3) age was 66 (56, 73) years with an age range of 31 to 93 years; 56.3% of the subjects were ≥ 65 years of age. Overall, 50.2% of the subjects were male, the majority of subjects were white (60.0%); and the majority of subjects identified as not Hispanic or Latino (76.3%). The median (Q1, Q3) baseline BMI was 25.9 (23.6, 29.6) kg/m^2. At study entry, 50.5% of subjects had a Karnofsky performance status (KPS) score of 80 or 90 and 5.1% 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 5.6 (3.4, 9.2) years, with a range of 0.05 to 26.6 years. Approximately two thirds of the subjects had FL (65.8%) and the remaining had other subtypes of iNHL, including SLL (9.2%), MZL (18.6%), and LPL/WM (6.4%). The majority of subjects (77.6%) 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 2.0 (1.0, 2.0), with a range of 1 to 10 for subjects in the IDL + R group and 1.0 (1.0, 2.0) with a range of 1 to 12 for subjects in the placebo + R group. The median (Q1, Q3) time since last prior regimen was 25.2 (14.9, 44.4) months for subjects in the IDL + R group and 25.8 (16.8, 48.4) months for subjects in the placebo + R 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 (95% CI) PFS was 23.8 (19.2, 24.7) months in the IDL + R group and 19.4 (16.4, 22.1) months in the placebo + R group, with an adjusted hazard ratio (HR; [95% CI]) of 0.50 (0.29, 0.85).

The median (95% CI) OS was not reached in either the IDL + R or placebo + R group; the adjusted HR (95% CI) was 4.74 (0.6, 37.12).

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 at 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 significant change in the IDLPK profile when coadministered with R.

Safety Results: In the Safety Analysis set, the median (Q1, Q3) duration of exposure to IDL in the IDL + R group was 6.0 (2.6, 11.1) months, with a range of 0.0 to 26.6 months. The median (Q1, Q3) duration of exposure to placebo in the placebo + R group was 9.6 (4.7, 16.4) months, with a range of 0.1 to 26.3 months.

The median (Q1, Q3) duration of exposure to rituximab was 6.4 (2.6, 8.1) months in the IDL + R group and 8.0 (4.3, 8.1) months in the placebo + R group.

The key safety findings are as follows:

Adverse Events: The percentage of subjects who experienced at least 1 AE during the study was similar in both treatment groups (98.5% [195 subjects] in the IDL + R group and (93.7% [89 subjects] in the placebo + R group). The most commonly reported AEs by PT in each treatment group were as follows:

- IDL + R: diarrhea (44.4%, 88 subjects), alanine aminotransferase (ALT) increased (35.9%, 71 subjects), and aspartate aminotransferase (AST) increased (30.8%, 61 subjects)
- Placebo + R: infusion related reaction (23.2%, 22 subjects), fatigue (21.1%, 20 subjects), and diarrhea (18.9%, 18 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 33 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, 19.2% (38 subjects) in the IDL + R group and 2.1% (2 subjects) in the placebo + R group had ≥ Grade 3 diarrhea and/or colitis. The exposure-adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.26 events/subject-year in the IDL + R group versus 0.02 events/subject-year in the placebo + R group. In the IDL + R group, the median (min, max) time to onset of the first ≥ Grade 3 event of diarrhea/colitis (n = 38) was 23.9 (0.3, 59.0) weeks, and the median (min, max) time to resolution of any ≥ Grade 3 diarrhea/colitis (n = 37) was 2.4 (0.7, 27.7) weeks. In the placebo + R group, the median (min, max) time to the onset of first ≥ Grade 3 event of diarrhea/colitis (n = 2) was 27.2 (3.3, 51.1) and the median (min, max) time to resolution of any ≥ Grade 3 diarrhea/colitis (n = 2) was 6.9 (0.1, 13.7) weeks. In the IDL + R group, 4.5% (9 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 used the PT of pneumonitis. In this study, 6.1% (12 subjects) in the IDL + R group and 1.1% (1 subject) in the placebo + R group had pneumonitis of any grade; 3.5% (7 subjects) of the IDL + R group and no subject in the placebo + R group experienced ≥ Grade 3 pneumonitis. The exposure-adjusted incidence rate for pneumonitis was 0.08 events/subject-year in the IDL + R group versus 0.01 events/subject year in the placebo + R group. In the IDL + R group, the median (min, max) time to onset of the first pneumonitis event of any grade (n = 12) was 12.9 (4.4, 49.1) weeks, and the median (min, max) time to resolution of any pneumonitis event (n = 11) was 5.1 (1.6, 40.0) weeks. In the placebo + R group, the pneumonitis event occurred at 34.4 weeks; this event was ongoing at the time of study discontinuation.

In the IDL + R group, 1.5% (3 subjects) had their study drug discontinued due to pneumonitis. No deaths due to pneumonitis were reported in this study.

≥ *Grade 3 Rash by MST*

Rash was defined per Gilead MST. In this study, 8.1% (16 subjects) in the IDL + R group and 1.1% (1 subject) in the placebo + R group had ≥ Grade 3 rash.

The exposure-adjusted incidence rate for ≥ Grade 3 rash was 0.10 events/subject-year in the IDL + R group versus 0.01 events/subject-year in the placebo + R group. In the IDL + R group, the median (min, max) time to onset of the first ≥ Grade 3 rash event (n = 16) was 2.8 (1.4, 59.3) weeks, and the median (min, max) time to resolution of any ≥ Grade 3 rash event (n = 14) was 2.1 (0.7, 10.0) weeks. In the placebo + R group, the ≥ Grade 3 rash event occurred at 1.1 weeks, with a time to resolution of 0.7 weeks.

In the IDL + R group, 2.5% (5 subjects) discontinued the study drug (IDL) due to ≥ Grade 3 rash.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported when IDL was administered concomitantly with other medications associated with these syndromes. No cases of SJS or TEN were reported in this study.

No deaths 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, 21.7% (43 subjects) in the IDL + R group and 4.2% (4 subjects) in the placebo + R group had ≥ Grade 3 infections. The exposure-adjusted incidence rate for ≥ Grade 3 infection was 0.31 events/subject-year in the IDL + R group versus 0.04 events/subject-year in the placebo + R group. In the IDL + R group, the median (min, max) time to onset of the first ≥ Grade 3 event of infection (n = 43) was 16.0 (0.7, 93.9) weeks, and the median (min, max) time to resolution of any ≥ Grade 3 infection (n = 41) was 1.3 (0.1, 53.6) weeks. In the placebo + R group, the median (min, max) time to onset of the first ≥ Grade 3 event of infection (n = 4) was 27.4 (9.9, 39.1) weeks, and the median (min, max) time to resolution of any ≥ Grade 3 infection (n = 3) was 0.7 (0.6, 2.1) weeks.

In the IDL + R group, 3.5% (7 subjects) discontinued the study drug (IDL) 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 1.0% (2 subjects) of the IDL + R group and no subject in the placebo + R group.

One subject (0.5%) in the IDL + R group died due to treatment-emergent infection (pneumonia). In addition, 1 subject (0.5%) in the IDL + R group died due to a febrile neutropenia event.

≥ Grade 3 Febrile Neutropenia

For the AEI of febrile neutropenia, the analysis utilized the single PT of febrile neutropenia. Overall, 3.0% (6 subjects) in the IDL + R group and no subject in the placebo + R group experienced ≥ Grade 3 febrile neutropenia. The exposure-adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.04 events/subject-year in the IDL+ R group versus no event in the placebo + R group. In the IDL + R group, the median (min, max) time to onset of the first ≥ Grade 3 event of febrile neutropenia (n = 6) was 14.9 (3.4, 50.7) weeks, and the median (min, max) time to resolution of any ≥ Grade 3 febrile neutropenia (n = 5) was 0.4 (0.3, 2.6) weeks.

In the IDL + R group, 1.0% (2 subjects) discontinued the study drug (IDL) due to ≥ Grade 3 febrile neutropenia. As noted above, 1 subject in the IDL + R group (0.5%) died due to a febrile neutropenia event.

Any Grade CMV Infection

For the AEI of CMV infection, the analysis utilized the entire high-level term (HLT) of cytomegaloviral infections and the PT of cytomegalovirus test positive. In this study, 1.0% (2 subjects) in the IDL + R group and no subject in the placebo + R group had CMV infection of any grade; both events of CMV infection were ≥ Grade 3.

The exposure-adjusted incidence rate for CMV infection was 0.01 events/subject-year in the IDL + R group versus no event in the placebo + R group. In the IDL + R group, the median (min, max) time to onset of the first CMV infection event of any grade (n = 2) was 13.1 (11.1, 15.1) weeks, and the median (min, max) time to resolution of any CMV infection event (n = 2) was 1.9 (1.0, 2.7) weeks. In the IDL + R group, no subject had their study drug dose (IDL) discontinued 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, 0.5% (1 subject) in the IDL + R group and no subject in the placebo + R group had PJP of any grade.

The exposure-adjusted incidence rate for PJP was 0.01 events/subject-year in the IDL + R group versus no event in the placebo + R group. The median time to onset of the PJP event was 45.1 weeks, and the median time to resolution of the event was 39.0 weeks. Study drug (IDL) was not discontinued due to PJP. No deaths due to PJP were reported in this study.

Deaths: In the IDL + R group, 11 subjects (5.6%) died: 8 subjects (4.0%) on study (between randomization and within 30 days from the end of the randomized, double-blind phase of the study), and 3 subjects (1.5%) during long-term follow-up (between randomization and 30 days from the end of the open-label extension phase). In the placebo + R group, no subject died on study; 2 subjects (2.1%) died during the long-term follow-up. Eight subjects (4.0%) in the IDL + R group and no subject in the placebo group experienced TEAEs that led to death. The TEAEs leading to death in the IDL + R group, were cachexia, cardiac arrest, chronic obstructive pulmonary disease (COPD), death, dyspnea, febrile neutropenia, hepatic failure, pneumonia, and pulmonary embolism each reported for 1 subject (0.5%).

Serious Adverse Events: There was an imbalance between the IDL + R and placebo + R groups in the percentage of subjects who had SAEs (52.0% versus 11.6%, 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 19.2% and 3.2% of subjects in the IDL + R and placebo + R groups, respectively) and gastrointestinal disorders (reported for 16.7% and 2.1% of subjects in the IDL + R and placebo + R groups, respectively). The most frequently reported SAEs by PT were as follows:

- IDL + R group: pneumonia (9.6%, 19 subjects), diarrhea (9.1%, 18 subjects), and ALT increased (5.6%, 11 subjects)
- Placebo + R: infusion related reaction and cardiac failure congestive (2.1%, 2 subjects, each)

Within the SOC of infections and infestations, the most frequently reported SAEs by PT were pneumonia (reported for 9.6% [19 subjects] and no subject in the IDL + R and placebo + R groups, respectively), sepsis (reported for 2.5% [5 subjects] and no subject in the IDL + R and placebo + R groups, respectively) and urinary tract infections (reported for 2.0% [4 subjects] and no subject in the IDL + R and placebo + R groups, respectively). A death due to treatment-emergent infection (pneumonia) was reported for 1 subject (0.5%) in the IDL + R group. In addition, 1 subject in the IDL + R 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 + R group than in the placebo + R group (44.4% [88 subjects] versus 7.4% [7 subjects], respectively). In the IDL + R group, AEs that led to study drug discontinuation in ≥ 2% of subjects included the following: diarrhea (8.6%, 17 subjects), ALT increased (5.1%, 10 subjects), AST increased (4.5%, 9 subjects), rash (4.0%, 8 subjects), pneumonia and vomiting (each in 2.0%, 4 subjects). In the placebo + R group, no event that led to study drug discontinuation was reported in ≥ 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. The median absolute neutrophil counts (ANC) over time remained stable in the total population of all treatment groups; neutrophil counts were steady- to slightly-improved over time in subjects with baseline neutropenia. In this study, 43.9% (87 subjects) in the IDL + R group had a decreased neutrophil count of any grade: 5.6% (11 subjects) had decreased neutrophil count of Grade 3 and 6.1% (12 subjects) of Grade 4. In the placebo + R group, 35.8% (34 subjects) had decreased neutrophil count of any grade: 5.3% (5 subjects) had decreases each of Grade 3 and Grade 4.

In this study, treatment-emergent elevations (all grades, per laboratory assessments) in serum ALT occurred in 72.7% (144 subjects) in the IDL + R group (≥ Grade 3 increases observed in 48.5% [96 subjects]) compared with 15.8% (15 subjects) in the placebo + R group (≥ Grade 3 increases were not observed). Treatment-emergent elevations in serum AST occurred in 69.7% (138 subjects) in the IDL + R group (≥ Grade 3 increases observed in 30.8% [61 subjects]) and 12.6% (12 subjects) in the placebo + R group (≥ Grade 3 increases were not observed). Overall, 30.8% (61subjects) had Grade 3 or 4 elevations in both ALT and AST in the IDL + R group. The Grade 3 or 4 ALT or AST elevations typically occurred within the first 3 months of therapy (median time to onset 5.1 weeks). In the IDL + R group, the observed Grade 3 or 4 elevations in ALT or AST for almost all subjects (94.8% [91 of 96 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 for both the IDL+R and the placebo + R treatment groups. The exposure adjusted incidence rates of hemoglobin abnormalities (all grades) were similar between the 2 treatment groups; exposure adjusted incidence rates for white blood cell (leukocyte and lymphocyte) abnormalities were generally higher in the IDL + R group than in the placebo + R group. The exposure adjusted incidence rates of abnormalities (all grades) were generally notably higher in the IDL + R group than in the placebo group for elevations in alkaline phosphatase (ALP) (0.51 versus 0.10 events/subject-year, respectively), ALT (2.17 versus 0.19 events/subject-year, respectively), AST (1.97 versus 0.13 events/subject-year, respectively), and gamma-glutamyl transferase (GGT) (1.26 versus 0.19 events/subject-year, respectively).

CONCLUSIONS:

This study was terminated early due to 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 R 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 + R and placebo + R groups in the percentage of subjects who had SAEs, particularly events in the SOC of infections and infestations (19.2% and 3.2%, respectively).
- The occurrence of AEIs related to infections was higher in the IDL + R group than the placebo + R group: ≥ Grade 3 infection (21.7% versus 4.2%, respectively), ≥ Grade 3 febrile neutropenia (3.0% versus 0.0%, respectively), any grade CMV infection (1.0% versus 0.0%, respectively), and any grade PJP (0.5% versus 0.0%, respectively).
- Eight subjects (4.0%) in the IDL + R group and no subjects in the placebo + R group experienced TEAEs that led to death. A death due to treatment-emergent infection (pneumonia) was reported for 1 subject (0.5%) in the IDL + R group. In addition, 1 subject (0.5%) in the IDL + R group died due to a febrile neutropenia event.