FINAL ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia	
Name of Test Drug:	Idelalisib (IDL, Zydelig®)	
Dose and Formulation:	Idelalisib 150 mg	
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-312-0123	
Phase of Development:	Phase 3	
IND No.: **EudraCT No.:**	101254 2013-003313-17	
ClinicalTrials.gov Identifier	NCT01980888	
Study Start Date:	05 February 2014 (First Subject Screened)	
Study End Date:	16 June 2016 (Last Subject Observation)	
Principal or Coordinating Investigator:	Name: Affiliation:	Nicole Lamanna, MD PPD
Gilead Responsible Medical Monitor:	Name: Telephone: Fax:	Henry Adewoye, MD PPD PPD
Report Date:	29 November 2016	

CONFIDENTIAL AND PROPRIETARY INFORMATION

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

STUDY SYNOPSIS

Study GS-US-312-0123
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination with Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia

Investigators: This study was a global multicenter study

Study Centers: A total of 137 sites, 91 with subjects enrolled, in North America, Australia, and Europe

Publications: Not applicable

Study Period:

05 February 2014 (First Subject Screened)
16 June 2016 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To evaluate the progression-free survival (PFS) in subjects with previously untreated chronic lymphocytic leukemia (CLL) who would otherwise be suitable for bendamustine and rituximab treatment as standard of care

The secondary objectives of this study were as follows:

- To evaluate the effect of the addition of idelalisib (IDL) to bendamustine and rituximab on minimal residual disease (MRD)
- To evaluate the effect of the addition of IDL to bendamustine and rituximab on the magnitude of response and to evaluate overall survival
- To describe the safety profile observed with the addition of IDL to bendamustine and rituximab
- To determine IDL/metabolite plasma concentrations

Methodology: Study GS-US-312-0123 was a Phase 3, randomized, double-blind, placebo-controlled, clinical trial that was conducted in North America, Australia, and Europe. The objective of the study was to evaluate the efficacy and safety of IDL in combination with BR in previously untreated adult subjects with CLL. Subjects were randomized 1:1 to IDL or placebo based on the following stratification factors: immunoglobulin heavy chain variable region (IgHV) mutation: unmutated (or IgHV3-21) versus mutated (or indeterminate) as determined by an independent central laboratory, Rai stage 0-II versus III-IV, and presence versus absence of 17p deletion in CLL cells as determined by an independent central laboratory.

Subjects received IDL 150 mg or matching placebo twice daily taken orally continuously for 96 weeks. The study drug, IDL and matching placebo, were supplied by Gilead.

All subjects received rituximab with a planned dosing regimen of 375 mg/m^2 intravenously on Day 1 (Week 0); thereafter 500 mg/m^2 intravenously on Day 29 (Week 4), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), and Day 141 (Week 20) for a total of 6 infusions.

All subjects were administered bendamustine intravenously at a starting dose of 90 mg/m^2/infusion on treatment Day 1 and 2 (Week 0), Day 29 and 30 (Week 4), Day 57 and 58 (Week 8), Day 85 and 86 (Week 12), Day 113 and 114 (Week 16), and Day 141 and 142 (Week 20) (up to 6 total cycles as tolerated).

Bendamustine or rituximab may have been continued even if the other agent was discontinued due to drug-specific toxicity. Subjects who were tolerating study drug (IDL/placebo) were to continue study drug even if bendamustine or rituximab were discontinued due to bendamustine- or rituximab-related toxicities or due to an inability to continue bendamustine or rituximab therapy.

Treatment duration with IDL/placebo was up to 96 weeks.

Treatment duration with rituximab and bendamustine was up to 21 weeks (maximum of 6 cycles).

The Screening period was 4 weeks and the treatment period was up to 96 weeks. Study assessments continued until disease progression; at that point an end of study (EOS) visit was conducted. After the EOS there was a safety follow-up period of 30 days leading into annual long-term follow-up visits.

Number of Subjects (Planned and Analyzed):
Planned: 280
Enrolled: 311
Analyzed: 311

Diagnosis and Main Criteria for Inclusion: The inclusion criteria to be eligible for participation in this study included:

1) Male or female ≥18 years of age.
2) Diagnosis of B-cell CLL, according to International Workshop on Chronic Lymphocytic Leukemia and documented within medical records.
3) No prior therapy for CLL other than corticosteroids for disease complications.
4) 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 (European Cooperative Oncology Group [ECOG] prognostic score (PS) of 2: inability to work or perform usual activities), or
        iii) Fevers >100.5°F or 38.0°C for ≥2 weeks without the evidence of infection, or
        iv) Night sweats for >1 month without evidence of infection.
5) Presence of measurable lymphadenopathy (defined as the presence of ≥1 nodal lesion that measures ≥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] confirmed by the Independent Review Committee [IRC]).
6) ECOG performance status of ≤2.
7) Required baseline laboratory data (within 28 days prior to randomization) as shown in the table below:

Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hematopoietic	ANC	≥1 x 10^9/L[a]
	Platelets	≥75 x 10^9/L[a]
	Hemoglobin	≥100 g/L (10.0 g/dL or 6.2 mmol/L)[a]
Hepatic	Serum total bilirubin	≤1.5 x ULN (unless elevated due to Gilbert syndrome or hemolysis)
	Serum ALT	≤2.5 x ULN
	Serum AST	
Renal	C_{Cr}[b]	≥40 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 is positive)

β-hCG=beta human chorionic gonadotropin; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DNA=deoxyribonucleic acid; CCr=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; RNA=ribonucleic acid; ULN=upper limit of normal.

a Grade ≥2 neutropenia, thrombocytopenia, or anemia is permitted if abnormality is related to bone marrow involvement with CLL (as documented by bone marrow biopsy/aspirate)

b As calculated by the Cockcroft-Gault formula or measured

c For women of child-bearing potential only; serum β-hCG pregnancy test must be negative during Screening and serum β-hCG pregnancy test or urine dipstick pregnancy test must be negative at enrollment

8) For female subjects of childbearing potential, willing to use a protocol-recommended method of contraception during heterosexual intercourse from the signing of informed consent throughout the study treatment period and up to 30 days from the last dose of IDL/placebo or bendamustine, or 12 months from the last dose of rituximab (whichever was later).

9) For male subjects of reproductive potential, having intercourse with females of childbearing potential, willing to use a protocol-recommended method of contraception during heterosexual intercourse from the randomization visit throughout the study treatment period and up to 6 months following the last dose of bendamustine or for 90 days following the last dose of IDL/placebo or 12 months from the last dose of rituximab (whichever is later) and to refrain from sperm donation from randomization throughout the study treatment period and up to 6 months following the last dose of bendamustine or for 90 days following the last dose of IDL/placebo or 12 months from the last dose of rituximab (whichever was later).

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

11) In the judgment of the investigator, participation in the protocol offers 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.

12) Willing and able to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions.

13) Evidence of a signed informed consent.

The exclusion criteria were:

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) surgically treated low-grade prostate cancer, or
   e) DCIS of the breast treated with lumpectomy alone.
4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for IDL, bendamustine, or rituximab.
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 (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could have adversely affected the safety of the subject or impaired the assessment of study results.
13) Patients who have received yellow fever vaccine within 30 days prior to randomization.
14) Patients who have undergone major surgery within 30 days prior to randomization.

Duration of Treatment: IDL/placebo was taken continuously up to 96 weeks.
Rituximab was administered up to a maximum of 6 infusions. Bendamustine was administered up to a maximum of 6 cycles.

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

IDL: 150 mg/dose taken orally twice daily starting on Day 1 and administered continuously thereafter. Lot numbers administered in this study:

IDL 150 mg: CV1308B1, CV1305B1, CV1402B1,

IDL 100 mg: CV1302C1, C1304D1

Placebo 150 mg: CV1306B1

Placebo 100 mg: CV1307B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: Lot numbers were not collected when commercial product was provided, and are therefore listed only in countries/sites where Gilead provided the reference therapy.

Rituximab: 375 mg/m^2 intravenously on Day 1 (Week 0); thereafter 500 mg/m^2 intravenously on Day 29 (Week 4), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), and Day 141 (Week 20) for a total of 6 infusions.

Lot numbers administered in this study: H0672B03, H0710B03, N7004B07, N7005B03, N7015B01, and N7027B04

Bendamustine: 90 mg/m^2/infusion was administered on treatment Day 1 and 2 (Week 0), Day 29 and 30 (Week 4), Day 57 and 58 (Week 8), Day 85 and 86 (Week 12), Day 113 and 114 (Week 16), and Day 141 and 142 (Week 20) (up to 6 total cycles as tolerated).

Lot numbers administered in this study: 114990, 116679, 119667, and B277

Criteria for Evaluation:

In March 2016, this study was terminated early based on an increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving IDL in combination with standard therapies compared with the control groups which was observed by the independent Data Monitoring Committee (DMC) in a pooled analysis of three 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). A letter was sent to all participating investigators on March 11, 2016, advising them of the findings and termination of the study. The last patient last visit (LPLV) occurred 16 June 2016.

Efficacy: Due to early study termination, the prespecified efficacy analyses were not conducted. An analysis of investigator-assessed PFS and overall survival (OS) was conducted using the unblinded data that triggered the DMC's safety concern (data cut date 15 January 2016). This analysis (with 23 PFS events) occurred approximately 20 months prior to the planned interim analysis (82 PFS events).

Pharmacokinetics/Pharmacodynamics:

Blood samples for pharmacokinetic (PK) analysis of IDL were collected during the study predose and at 1.5 hours after IDL dose 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: Plasma concentrations of IDL and its major metabolite were listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, % coefficient of variation, standard deviation, median, minimum, Q1, Q3, and maximum).

Safety: Adverse event data were listed by subject. Treatment-emergent AEs, treatment-related AEs, serious AEs (SAEs), and AEs leading to permanent study drug discontinuation were summarized by treatment, system organ class, and preferred term using the current version of the Medical Dictionary for Regulatory Activities version 19.0. Listings of individual subject laboratory results were provided. Laboratory results and change from predose values for selected lab tests were summarized by treatment at scheduled visits. The incidence of treatment-emergent laboratory abnormalities was summarized by treatment.

Vital signs data were summarized by treatment.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: This study was fully enrolled at the time it was terminated for safety reasons. A total of 311 subjects were included in the Intent to Treat (ITT) Analysis Set in Study GS-US-312-0123, which includes all subjects who were randomized in the study regardless of whether they received study drug. This included 157 subjects in the IDL + BR group and 154 subjects in the placebo + BR based on a 1:1 randomization ratio when the study was terminated. Last patient last visit occurred on 16 June 2016. In the IDL + BR group, 13 subjects (8.3%) met the primary endpoint of the study (disease progression confirmed by the IRC or death), 17 subjects (10.8%) withdrew consent, 8 subjects (5.1%) were withdrawn by the investigator, and 3 subjects (1.9%) discontinued due to non-compliance with the study drug. The remaining 116 subjects (73.9%) discontinued when the study was terminated by the Sponsor. In the placebo + BR group, 21 subjects (13.6%) met the primary endpoint, 6 subjects (3.9%) withdrew consent, 3 subjects (1.9%) were withdrawn by the investigator, and 2 subjects (1.3%) discontinued due to non-compliance with the study drug. The remaining 122 subjects (79.2%) discontinued when the study was terminated by the Sponsor.

Consistent with the advanced age typical of the general CLL population, most subjects in the IDL + BR group (52.2%) were ≥ 65 years of age, with a median age of 65 years and range of 37 to 83 years. Most subjects in the IDL + BR group (63.7%) were male and most (96.8%) were white. Black/African American subjects comprised 0.6% of subjects, and no subjects were classified with race “Not Permitted” (ie, not permitted to report). The median (Q1, Q3) baseline BMI was 27.6 (24.3, 31.8) kg/m^2 in the IDL + BR group. Most subjects in the IDL + BR group (82 subjects; 52.2%) had an ECOG PS of 0.

Most subjects in the placebo + BR group (50.6%) were < 65 years of age, with a median age of 64 years and range of 30 to 83 years. Most subjects in the placebo + BR group (68.8%) were male and most (97.4%) were white. Black/African American subjects comprised 0.6% of subjects, and 1.3% of subjects were classified with race "Not Permitted" (ie, not permitted to report). The median (Q1, Q3) baseline BMI was 27.5 (24.8, 30.2) kg/m^2 in the placebo + BR group. In the placebo + BR group (77 subjects; 50.0%) had an ECOG PS of 0.

In the IDL + BR group, 59.9% of subjects had Rai Stage 0-II, 65.0% of subjects had unmutated IgHV, and 93.0% of subjects did not have 17p deletion. In the placebo + BR group, 57.2% of subjects had Rai Stage 0-II, 64.9% of subjects had unmutated IgHV, and 94.2% of subjects did not have 17p deletion.

Prior to study entry, the subject population had presented with CLL for a median (Q1, Q3) of 28.5 (9.2, 63.0) months with a range of 0.3 to 423.2 months. Other disease characteristics were balanced between treatment groups.

Efficacy Results: An analysis of investigator-assessed PFS and OS was conducted using the unblinded data that triggered the DMC's safety concern (data cut date 15 January 2016). The median (95% CI) investigator-assessed PFS was not reached in either the IDL + BR group or placebo + BR group with adjusted hazard ratio (HR [95% CI]) of 1.10 (0.48, 2.52).

The median (95% CI) OS was not reached in either the IDL + BR group or the placebo + BR group, with an adjusted HR (95% CI) of 3.34 (1.08, 10.39).

Pharmacokinetics/Pharmacodynamics Results: Trough concentrations of IDL and its major metabolite, GS-563117, were comparable at predose or 1.5 hours postdose between Week 2 and Week 20. Trough concentrations were similar to those observed in other monotherapy studies (eg, Study 101-02) and to population pharmacokinetic (PK) modeling estimates following IDL 150 mg twice daily monotherapy. These results suggest that there is no significant change in idelalisib PK when coadministered with bendamustine and rituximab.

Safety Results: In the Safety Analysis Set, the median (first quartile, third quartile [Q1, Q3]) duration of exposure to IDL in the IDL + BR group was 12.1 (3.1, 15.0) months, with a range of 0.2 to 22.1 months. Overall, the median (Q1, Q3) exposure was 12.8 (7.2, 15.6) months with a range of 0.2 to 22.1 months.

The median (Q1, Q3) duration of exposure to bendamustine was 4.7 (2.8, 5.2) months in the IDL + BR group and 4.7 (4.7, 5.1) months in the placebo + BR group.

The median (Q1, Q3) duration of exposure to rituximab was 4.7 (3.1, 5.3) months in the IDL + BR group and 4.7 (4.6, 5.1) months in the placebo + BR group.

Key safety findings are as follows:

AEs: Adverse events were common in both groups, occurring in 100.0% (156 subjects) of the IDL + BR group and 99.4% (153 subjects) of the placebo + BR group. The most commonly reported AEs by treatment group were as follows:

- IDL + BR: pyrexia (55.8%, 87 subjects), neutropenia (54.5%, 85 subjects), and diarrhea (42.3%, 66 subjects)
- Placebo + BR: neutropenia (58.4%, 90 subjects), nausea (40.9%, 63 subjects), and pyrexia (33.8%, 52 subjects)

The AE with the largest difference reported (22.0%) in the IDL + BR group compared to the placebo + BR group was pyrexia. Pyrexia was reported in 55.8% (87 subjects) in the IDL + BR group and 33.8% (52 subjects) in the placebo + BR group.

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

- IDL + BR: neutropenia (1.20 events/subject-year), pyrexia (1.17 events/subject-year), rash (0.70 events/subject-year), and diarrhea (0.68 events/subject-year)
- Placebo + BR: neutropenia (0.94 events/subject-year), nausea (0.54 events/subject-year), and pyrexia (0.38 events/subject-year)

Subjects in the placebo + BR group had an adjusted incidence rate of 0.32 events/subject-year for diarrhea and subjects in the IDL + BR group had an adjusted incidence rate of 0.64 events/subject-year for nausea.

AEIs: AEs of interest for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade progressive multifocal leukoencephalopathy [PML]), any grade pneumonitis, and ≥ Grade 3 rash by MST. Following from safety findings identified in March 2016, the AEI list was expanded to include infection (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade CMV infection, and any grade PJP).

No subjects in either treatment group reported any form of bowel perforation or event of PML in this study.

Diarrhea/Colitis

The analysis for diarrhea and/or colitis utilized the combined PTs of diarrhea and colitis. In this study, 14 subjects (9.0%) in the IDL + BR group and 5 subjects (3.2%) in the placebo + BR group had ≥ Grade 3 diarrhea and/or colitis. The exposure-adjusted incidence rate for ≥ Grade 3 diarrhea and/or colitis was 0.10 events/subject-year in the IDL + BR group versus 0.03 events/subject-year in the placebo + BR group. In the IDL + BR group, 1 subject (0.6%) had their study drug dose reduced, 6 subjects (3.8%) had an interruption in study drug, and 2 subjects (1.3%) discontinued study drug (IDL) due to ≥ Grade 3 diarrhea and/or colitis. No deaths due to diarrhea and/or colitis were reported in this study.

Pneumonitis

In the analysis for pneumonitis, 10 subjects (6.4%) in the IDL + BR group and 4 subjects (2.6%) in the placebo + BR group had pneumonitis of any grade. The exposure-adjusted incidence rate for pneumonitis was 0.07 events/subject-year in the IDL + BR group versus 0.02 events/subject-year in the placebo + BR group. In the IDL + BR group, no subject had study drug dose reduced, 3 subjects (1.9%) had an interruption in study drug, and 3 subjects (1.9%) discontinued study drug (IDL) due to pneumonitis. In the placebo + BR group, no subject had a dose reduction, 1 subject (0.6%) had interruption of study drug, and 1 subject (0.6%) discontinued study drug (placebo) due to pneumonitis. No death was reported due to pneumonitis.

Rash

Rash was defined per Gilead MST. In this study, 26 subjects (16.7%) in the IDL + BR group and 16 subjects (10.4%) in the placebo + BR group had ≥ Grade 3 rash. The exposure-adjusted incidence rate for ≥ Grade 3 rash was 0.21 events/subject-year in the IDL + BR group versus

0.10 events/subject-year in the placebo + BR group. In the IDL + BR group, 2 subjects (1.3%) had their study drug dose reduced, 16 subjects (10.3%) had an interruption in study drug, and 6 subjects (3.8%) discontinued study drug (IDL) due to ≥ Grade 3 rash. In the placebo + BR group, 2 subjects (1.3%) had their study drug dose reduced due to ≥ Grade 3 rash; 7 subjects (4.5%) had an interruption in study drug, and no subjects discontinued study drug (placebo) due to ≥ Grade 3 rash. No deaths due to rash were reported in this study.

Infections

The analysis for ≥ Grade 3 infection utilized the system organ class (SOC) of infections and infestations and the PT of febrile neutropenia. A total of 71 subjects (45.5%) in the IDL + BR group and 31 subjects (20.1%) in the placebo + BR group had ≥ Grade 3 infections in this study. The exposure-adjusted incidence rate for ≥ Grade 3 infection was 0.74 events/subject-year in the IDL + BR group versus 0.19 events/subject-year in the placebo + BR group. In the IDL + BR group, 1 subject (0.6%) had their study drug dose reduced, 28 subjects (17.9%) had an interruption in study drug, and 13 subjects (8.3%) discontinued study drug (IDL) due to ≥ Grade 3 infection. A total of 8 subjects in the IDL + BR group and 1 subject in the placebo + BR group died due to infection.

Febrile Neutropenia

An imbalance in the incidence of ≥ Grade 3 febrile neutropenia between the 2 treatment groups was observed in this study: 33 subjects (21.2%) in the IDL + BR group and 16 subjects (10.4%) in the placebo + BR group experienced ≥ Grade 3 febrile neutropenia. The exposure-adjusted incidence rate for ≥ Grade 3 febrile neutropenia was 0.29 events/subject-year in the IDL + BR group versus 0.09 events/subject-year in the placebo + BR group. In the IDL + BR group, no subjects had their study drug dose reduced, 15 subjects (9.6%) had an interruption in study drug, and 1 subject (0.6%) discontinued study drug (IDL) due to ≥ Grade 3 febrile neutropenia. No deaths were attributed to febrile neutropenia were reported in this study.

CMV

The analysis for CMV infection in this study utilized either the high level term (HLT) of cytomegaloviral infections or the preferred term (PT) of cytomegalovirus test positive. In this study, 8 subjects (5.1%) in the IDL + BR group and 2 subjects (1.3%) in the placebo + BR group had CMV infection of any grade. The exposure-adjusted incidence rate for CMV infection was 0.06 events/subject-year in the IDL + BR group versus 0.01 events/subject-year in the placebo + BR group. In the IDL + BR group, no subjects had their study drug dose reduced, 4 subjects (2.6%) had an interruption in study drug, and 2 subjects (1.3%) discontinued study drug (IDL) due to CMV infection. One death (0.6%) due to CMV infection, in a subject in the IDL + BR group, was reported in this study.

PJP

The analysis for PJP utilized the HLT of *Pneumocystis* infections. In this study, 2 subjects (1.3%) in the IDL + BR group and no subject in the placebo + BR group had PJP of any grade. In the IDL + BR group, 1 subject (0.6%) had an interruption in study drug due to PJP. No death was reported due to PJP infection.

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

In this study, 63.5% (99 subjects) of the IDL + BR group had treatment-emergent alanine aminotransferase (ALT) laboratory abnormalities of any grade (26.3% [41 subjects] with ≥ Grade 3 abnormalities), compared with 33.8% (52 subjects) of the placebo + BR group (1.3% [2 subjects] with ≥ Grade 3 abnormalities). For aspartate aminotransferase (AST), 60.9% (95 subjects) of the IDL + BR group had treatment-emergent abnormalities of any grade (16.7% [26 subjects] with ≥ Grade 3 abnormalities), compared with 28.6% (44 subjects) of the placebo + BR group (1.3% [2 subjects] with ≥ Grade 3 abnormalities). A total of 16.7% (26 subjects) of the IDL + BR group had treatment-emergent Grade 3 or 4 ALT and AST increases, compared with 1.3% (2 subjects) of the placebo + BR group. The exposure-adjusted incidence rate of treatment-emergent laboratory abnormalities of any grade ALT increase was 1.66 events/subject-year in the IDL + BR group and 0.36 events/subject-year in the placebo + BR group. The exposure-adjusted incidence rate of treatment-emergent laboratory abnormalities of any grade AST increase was 1.46 events/subject-year in the IDL + BR group and 0.30 events/subject-year in the placebo + BR group.

For the 41 subjects (26.3%) in the IDL + BR group with Grade 3 or 4 ALT and/or AST elevations, the median (min, max) time to onset of the first Grade 3 or 4 event was 6.7 (2.1, 24.1) weeks. Thirty-nine of the 41 subjects (95.1%) had a median (min, max) time to resolution (≤ Grade 1) of 3.1 (1.1, 12.3) weeks. The 2 subjects without resolution discontinued from study treatment: 1 due to an AE of Cytomegalovirus infection, 1 due to an AE of acute renal failure. One subject in the IDL + BR group (subject PPD and no subjects in the placebo + BR group experienced AST or ALT > 3 × upper limit of normal (ULN) with concurrent elevation of bilirubin > 2 × ULN and elevated (> 1.5 ULN) alkaline phosphatase.

In this study, 84.6% (132 subjects) of the IDL + BR group and 87.0% (134 subjects) of the placebo + BR group had treatment-emergent laboratory assessments of decreased neutrophil count. Overall, 65.4% (102 subjects) of the IDL + BR group and 64.3% (99 subjects) of the placebo + BR group had ≥ Grade 3 treatment-emergent decreased neutrophil count. The exposure-adjusted incidence rate of laboratory abnormalities of any grade neutropenia was 4.72 events/subject-year in the IDL + BR group and 3.24 events/subject-year in the placebo + BR group.

Deaths: Through the 17 August 2016 database finalization date, 18 deaths were reported: 15 during the study and 3 during long-term follow-up. In the IDL + BR group, 8.3% (13 subjects) died, 7.7% (12 subjects) on study (deaths between randomization and within 30 days following end of study) and 0.6% (1 subject) during long-term follow-up. In the placebo + BR group, 3.2% (5 subjects) died, 1.9% (3 subjects) on study and 1.3% (2 subjects) during long-term follow-up.

SAEs: Serious AEs were more common in the IDL + BR group, and reported for 72.4% (113 subjects) in the IDL + BR group and 44.2% (68 subjects) of the placebo + BR group. Serious AEs were typical of the population, with events occurring most commonly in the SOC of infections and infestations (32.1% [50 subjects] in the IDL + BR group and 10.4% [16 subjects] in the placebo + BR group) followed by blood and lymphatic system disorders (28.2% [44 subjects] in the IDL + BR group and 11.7% [18 subjects] in the placebo + BR group).

The most frequently reported SAEs by PT were as follows:

- IDL + BR group: febrile neutropenia (18.6%, 29 subjects), pyrexia (16.7%, 26 subjects), and pneumonia (7.1%, 11 subjects).
- Placebo + BR: pyrexia (12.3%, 19 subjects), febrile neutropenia (10.4%, 16 subjects), and pneumonia (3.9%, 6 subjects).

AEs Leading to Discontinuation of Study Drug: Overall, 38.5% (60 subjects) of the IDL + BR group and 7.8% (12 subjects) of the placebo + BR group discontinued study drug (IDL/placebo) due to an AE. Diarrhea led to study drug discontinuation in 3.8% (6 subjects) in the IDL + BR group and 1.3% (2 subjects) in the placebo + BR group, sepsis led to study drug discontinuation in 3.2% (5 subjects) in the IDL + BR group and no subject in the placebo + BR group, and rash led to study drug discontinuation in 3.2% (5 subjects) in the IDL + BR group and 0.6% (1 subject) of the placebo + BR group.

Clinical Laboratory Evaluations:

The most common treatment-emergent ≥ Grade 3 serum chemistry abnormality was increased ALT, occurring in 26.3% of subjects in the IDL + BR group and 1.3% of subjects in the placebo + BR group, followed by increased AST, occurring in 16.7% of subjects in the IDL + BR group and 1.3% of subjects in the placebo + BR group. The adjusted rates of abnormalities (all grades) were generally higher in the IDL + BR group most notably for elevations in ALT, AST, and triglycerides.

Hemoglobin concentrations and platelet counts trended upward with time for both treatment groups. Median neutrophil counts were generally stable over time in both treatment groups. Decreased lymphocytes (any grade) were the most common treatment-emergent hematologic abnormality overall, occurring in 87.8% (137 subjects) of the IDL + BR group and 92.2% (142 subjects) of the placebo + BR group. Grade 3 or 4 decreased lymphocytes were observed in 71.8% (112 subjects) of the IDL + BR group and 71.4% (110 subjects) of the placebo + BR group. The adjusted rates of most hematologic abnormalities (all grades) were similar between the 2 treatment groups.

CONCLUSIONS:

This study was terminated early due to a safety signal. At the time point of the safety findings, an analysis of investigator-assessed PFS/and OS was conducted to inform the potential benefit-risk assessment of treatment in both groups. At this early point in the study, the risk outweighed the benefit for both PFS and OS. 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 would have been expected to emerge. Because the factors contributing to the AEs were not completely understood, the decision was made to terminate this study. Due to early study termination, the prespecified efficacy analyses were not conducted.

The safety 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 (32.1% and 10.4%, respectively).
- The occurrence of AEIs related to infections was higher in the IDL + BR group than the placebo + BR group: ≥ Grade 3 infection (45.5% versus 20.1%, respectively), ≥ Grade 3 febrile neutropenia (21.2% versus 10.4%, respectively), any grade CMV infection (5.1% versus 1.3%, respectively), and any grade PJP (1.3% versus 0.0%, respectively).

Twelve subjects (7.7%) in the IDL + BR group and 3 subjects (1.9%) in the placebo + BR group experienced TEAEs that led to death. Death due to treatment-emergent infections was reported for 8 subjects (5.1%) in the IDL + BR group (4 due to sepsis and 1 each due to CMV infection, neutropenic sepsis, pneumonia, and septic shock), and 2 of these subjects listed the actual cause of death as respiratory distress (Subject PPD and cardiac arrest (Subject PPD One subject (0.6%) in the placebo + BR group died due to treatment-emergent infection (due to strongyloidiasis).