FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2 Study to Assess the Efficacy and Safety of Idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents
Name of Test Drug:	Idelalisib (IDL, Zydelig®, GS-1101, formerly CAL-101)
Dose and Formulation:	Dose: 150 mg twice daily (2 × 75-mg tablets or 1 × 150-mg tablet) 100 mg twice daily (1 × 100-mg tablet) 75 mg twice daily (1 × 75-mg tablet)
Indication:	Indolent B-cell non-Hodgkin lymphoma (iNHL) refractory to rituximab and alkylating agents
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	101-09
Phase of Development:	Phase 2
IND No.:	101254
EudraCT No.:	2010-022155-33
ClinicalTrials.gov Identifier:	NCT01282424
Study Start Date:	18 March 2011 (First Subject Screened)
Study End Date:	25 June 2013 (Last Subject Last Observation for the Primary Endpoint) 16 May 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Ajay K Gopal, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Aaron Weitzman, MD Telephone: PPD
Report Date:	13 May 2019
Previous Report Date(s):	12 August 2013

STUDY SYNOPSIS
Study 101-09
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2 Study to Assess the Efficacy and Safety of Idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents

Investigators: Multicenter study

Study Centers: 54 sites of which 41 enrolled patients in North America and Europe

Publications:

Salles G, Kahl B, de Vos S, Wagner-Johnston N, Schuster S, Jurczak W, et al. Interim Results from a phase 2 study of PI3K-delta inhibitor idelalisib in patients with relapsed indolent non-Hodgkin lymphoma (iNHL) refractory to both rituximab and an alkylating agent [Presentation]. 13th International Conference on Malignant Lymphoma (ICML); 2013 June 19-22; Lugano, Switzerland.

Gopal AK, Kahl BS, de Vos S, Wagner-Johnston, Schuster SJ, Jurczak WJ, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014; 370(11):1008-1018. doi: 10.1056NEJMoa1314583. Epub 2017 Jan22.

Gopal AK, Kahl BS, Flowers CR, Martin P, Ansell SM, Abella-Dominicis E, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. Blood. 2017; 129(2): 3037-3039.

Salles G, Schuster SJ, de Vos S, Wagner-Johnston ND, Viardot A, Blum KA, et al. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. Haematologica. 2017;102: e159.

Study Period:

18 March 2011 (First Subject Screened)

25 June 2013 (Last Subject Last Observation for the Primary Endpoint)

16 May 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 2

Objectives:

The primary objective of this study was as follows:

- To evaluate tumor regression as determined by overall response rate (ORR) in subjects receiving idelalisib (IDL, GS-1101, Zydelig®) for treatment of indolent non-Hodgkin lymphoma (iNHL) refractory to rituximab and alkylating agents

The secondary objectives of this study were as follows:

- To determine the onset, magnitude, and duration of tumor control and of treatment success in subjects receiving IDL
- To characterize health-related quality of life (HRQL) as reported by subjects with iNHL receiving IDL
- To evaluate the effects of IDL on subject performance status
- To assess the pharmacodynamic effects of IDL
- To evaluate IDL treatment administration and compliance with IDL therapy
- To describe the safety profile of IDL
- To characterize IDL plasma exposure over time
- To generate pharmacokinetic (PK) data with the final tablet formulation of IDL in subjects with iNHL (through conduct of a PK substudy)

Methodology: This was a Phase 2, open-label, single-arm, 2-stage, efficacy, safety, PK, and pharmacodynamic study of IDL in subjects with previously-treated iNHL that was refractory both to rituximab and to alkylating-agent-containing chemotherapy.

Number of Subjects (Planned and Analyzed):
Planned: ≥ 100 evaluable subjects

Analyzed:

- Intent-to-treat (ITT) Analysis Set: 125 subjects
  - ITT: Follicular lymphoma (FL): 72 subjects

Diagnosis and Main Criteria for Inclusion:

- Histologically confirmed diagnosis of B-cell iNHL (FL, small lymphocytic lymphoma [SLL], lymphoplasmacytic lymphoma [LPL] with or without associated Waldenstrom macroglobulinemia [WM], marginal zone lymphoma [MZL])
- Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy
- Lymphoma that was refractory to rituximab and to an alkylating agent. (Refractory status was defined as lack of response to, or progression within 6 months of completion of therapy.)

Duration of Treatment: Subjects received IDL until the occurrence of any events requiring treatment discontinuation (eg, disease progression, pregnancy, noncompliance).

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

Dose:

- IDL 150 mg twice daily
  - 2 × 75-mg oral tablets (Batch No. B100382) or
  - 1 × 150-mg oral tablet. (Batch Nos. B100735, CV1107D2, CV1110D1, CV1308B1, CV1603B1, CY1202B1, PCZD)

Possible dose reductions if required by IDL-related adverse events (AEs):

- Reduced Dose −1: IDL 100 mg twice daily, 1 × 100 mg oral tablet (Batch Nos. B100326, CV1304C1, CY1201B1, NSZP, PCZC, PCZX)
- Reduced Dose −2: IDL 75 mg twice daily, 1 × 75 mg oral tablet (Batch No. B100382)

Reference Therapy, Dose, Mode of Administration, and Batch No.: None

Criteria for Evaluation:

Efficacy: Efficacy was assessed by:

- Overall response rate (ORR) - defined as the proportion of subjects who achieved a confirmed complete response (CR) or partial response (PR or minor response [MR] for subjects with WM) during IDL treatment
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR (or MR for subjects with WM) to the earlier of the first documentation of disease progression or death from any cause
- Lymph node response rate – defined as the proportion of subjects who achieve a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions
- Time to response (TTR) – defined as the interval from the start of IDL treatment to the first documentation of CR or PR (or MR for subjects with WM)
- Progression-free survival (PFS) – defined as the interval from the start of IDL treatment to the earlier of the first documentation of disease progression or death from any cause
- Overall Survival (OS) – defined as the interval from the start of IDL treatment to death from any cause
- Changes in HRQL as reported by subjects using the Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym)
- Changes in performance status as documented using the Karnofsky performance status criteria
- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug

Pharmacokinetics/Pharmacodynamics: Pharmacokinetics and pharmacodynamics were assessed by:

- IDL trough and peak plasma concentrations assessed predose and 1.5 hours postdose on Days 1, 29, 57, and 113
- Pharmacokinetic parameters (AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, C_{last}, T_{max}, T_{last}, $t_{1/2}$, λ_z , CL/F, V_z/F, C_{tau} [multiple-dose], and AUC_{tau} [multiple-dose]) on Days 1 and 29 (for subjects in the PK substudy)
- Changes in the plasma concentrations of disease-associated chemokines and cytokines

Safety: Safety was assessed by the type, frequency, severity, timing, and relationship to study therapy of any AEs or abnormalities of physical findings, laboratory tests, or electrocardiograms; drug discontinuations due to AE; or serious adverse events (SAEs)

Statistical Methods:

Efficacy: Data were presented for both the investigator assessments and the Independent Review Committee (IRC) assessments, with the latter considered primary for analyses of ORR and other tumor control endpoints. Consistency of evaluation between IRC and investigator assessments was summarized by the percent agreement in overall response.

The primary endpoint, ORR, was defined as the proportion of subjects who achieved a CR or PR (or MR for subjects with WM) during the IDL treatment. The study tested the hypothesis that ORR was ≥ 39% (ie, ≥ ~40%) against the null hypothesis that was ≤ 20%. The ORR and 95% confidence interval (CI) were presented along with the corresponding p-value from the exact binomial test.

Secondary endpoints DOR (based on responding subjects) and PFS were summarized using the Kaplan-Meier (KM) method. The date of definitive progression was the time point at which progression was first identified by relevant radiographic or pathology data. Death occurring ≤ 30 days following the discontinuation of study drug was considered as an event for the DOR and PFS calculation. Data were censored on the date of the last tumor assessment (including assessments with a not evaluable outcome) for subjects (1) who did not have progressive disease (PD) or die within 30 days of permanent study drug discontinuation, (2) who started new antitumor therapy prior to PD, or (3) had ≥ 2 consecutive missing tumor assessments before PD or death. Subjects without adequate baseline tumor response evaluation were censored on Study Day 1.

Lymph node response rate was summarized with 95% CI based on the binomial distribution in the ITT Analysis Set. The SPD and percent change in SPD from baseline to each subsequent assessment were summarized, in addition to the best percent change from baseline during the study.

Time to response was summarized based on responding subjects using descriptive statistics.

Overall survival was analyzed using the KM method based on the ITT Analysis Set. An on-study OS analysis was performed by only including deaths that occurred while a subject was on study treatment or within 30 days after the last study treatment. Overall survival was also analyzed by including the long-term follow-up data, considering any death as an event. Data from surviving subjects were censored at the last time that the subject was known to be alive.

The FACT-Lym questionnaire was scored as recommended in the user manual for the instrument. The mean subscale scores, the sum of the scores from physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns, were summarized in addition to change from baseline and best change from baseline. The following composite scores were derived from the data above: FACT-Lym Trial Outcome Index, Functional Assessment of Cancer Therapy-General (FACT-G) Total Score, and FACT-Lym Total Score.

The Karnofsky performance status scores and change from baseline scores to each subsequent assessment were summarized, in addition to the best and worst changes from baseline during the study.

Pharmacokinetics/Pharmacodynamics: Plasma concentrations collected prior to the morning dose and 1.5 hours postdose (morning) were summarized. Pharmacokinetic parameters were estimated using noncompartmental methods for the PK substudy.

The concentration of each pharmacodynamic variable at each assessment and the change from baseline to each assessment were summarized, in addition to the best change from baseline during the study.

Safety: Adverse events were classified by Medical Dictionary for Regulatory Activities, Version 21.0. The severity of AEs was graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Investigators assessed each AE with respect to its relatedness to study drug as definite, probable, possible, unlikely, or unrelated. An AE was classified as related to study drug treatment if the investigators' assessment was reported as definite, probable, or possible.

All AEs were listed, and treatment-emergent AEs were summarized. A treatment-emergent AE was defined as an AE that occurred or worsened in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study, or a continuing AE diagnosed prior to the start of treatment and worsening in severity grade after the start of treatment, a non-serious AE at baseline becoming serious after the start of treatment, or an AE resulting in treatment discontinuation after the start of treatment.

Listings and summaries were prepared for treatment-emergent AEs classified by severity (Grade 3 or higher); AEs reported as related to study drug by investigators; AEs leading to treatment interruption, modification, or discontinuation; and SAEs.

All laboratory data were listed, and treatment-emergent laboratory abnormalities were summarized. A treatment-emergent laboratory abnormality was defined as an abnormality that, compared to baseline, worsened by ≥ 1 grade in the period from the first dose of study drug to 30 days after the last dose of study drug. Hematological, serum biochemistry, and urine data and changes from baseline (only for continuous laboratory parameters) were summarized by visit and presented by CTCAE severity grade with corresponding percentages. Shift tables for hematology and serum biochemistry were presented showing change in CTCAE severity grade from baseline to worst grade postbaseline.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 125 subjects enrolled in the study. Seventy-nine subjects (63.2%) completed treatment (70 subjects [56.0%] due to PD and 9 subjects [7.2%] due to death), and 46 subjects (36.8%) discontinued treatment. Among the 125 subjects enrolled in the study, 30 subjects (24.0%) discontinued due to AEs, 6 subjects (4.8%) withdrew consent, 7 subjects (5.6%) discontinued at the request of the investigator, and 3 subjects (2.4%) discontinued due to "other."

Long-term post-treatment follow-up was measured from the last dose of study drug. Of the 125 subjects enrolled in the study, 84 subjects (67.2%) entered long-term follow-up and 20 subjects (16.0%) completed long-term follow-up. Among the 64 subjects (51.2%) who discontinued long-term follow-up, 40 subjects (32.0%) discontinued due to death. Other reasons for discontinuation in long-term follow-up included withdrawal of consent (2 subjects, 1.6%), lost to follow-up (1 subject, 0.8%), and other (21 subjects, 16.8%). A total of 82 subjects (65.6%) of the originally enrolled 125 subjects completed 6 months of long-term follow-up and 30 subjects (24.0%) completed 5 years of long-term follow-up.

A total of 72 subjects with FL enrolled in the study. Forty-six subjects with FL (63.9%) completed treatment (41 subjects [56.9%] due to PD and 5 subjects [6.9%] due to death), and 26 subjects (36.1%) discontinued treatment. Among those who discontinued treatment, 15 subjects (20.8%) discontinued due to AEs, 5 subjects (6.9%) withdrew consent, 4 subjects (5.6%) discontinued at the request of the investigator, and 2 subjects (2.8%) discontinued due to "other."

Of the 72 subjects with FL enrolled in the study, 53 subjects (73.6%) entered long-term follow-up and 15 subjects (20.8%) completed long-term follow-up. Among the 38 subjects (52.8%) who discontinued long-term follow-up, 24 subjects (33.3%) discontinued due to death. Other reasons for discontinuation in long-term follow-up included withdrawal of consent (1 subject, 1.4%), lost to follow-up (1 subject, 1.4%), and other (12 subjects, 16.7%). Of the 72 total enrolled subjects with FL, 52 subjects (72.2%) completed 6 months of long-term follow-up, and 23 subjects (31.9%) completed 5 years of long-term follow-up.

Overall, subject age ranged from 33 to 87 years with a median of 64 years. The majority of subjects were male (80 subjects [64.0%]) and white (110 subjects [88.0%]). The median (range) number of prior treatment regimens received was 4 (2 to 12), with 73 subjects (58.4%) treated with 4 or more prior regimens. All subjects were refractory to rituximab and 124 subjects (99.2%) were refractory to an alkylating agent. A total of 99 subjects (79.2%) were refractory to 2 or more prior regimens. Fifty-four subjects (43.2%) were unsuited for radioimmunotherapy due to their baseline hematological status. A total of 72 subjects (57.6%) had FL, 28 subjects (22.4%) had SLL, 10 subjects (8.0%) had LPL/WM, and 15 subjects (12.0%) had MZL. Median (range) time since diagnosis was 5.3 (0.4, 18.4) years. Most subjects (87 subjects [69.6%]) were Ann Arbor Stage IV at diagnosis. Median (range) diameter of the largest lesion at baseline was 4.7 (2.0, 25.0) cm. Most subjects (73.6%) had lesions ≥ 2 cm to < 7 cm in diameter at baseline; 26.4% of subjects had bulky lesions (≥ 7 cm) at baseline.

Efficacy Results:

Overall Response Rate:
The ORR based on IRC assessment for all subjects (N = 125) was 57.6% (n = 72): 13 subjects (10.4%) had a best overall response (BOR) of CR, 58 subjects (46.4%) had a BOR of PR, and 1 subject (0.8%) with WM had a BOR of MR. The ORR based on investigator assessment (60.0%) was in agreement with that of the IRC: 8 subjects (6.4%) had a BOR of CR and 66 subjects (52.8%) had a BOR of PR. The IRC and the investigator agreed in their assessment of overall response for 88% of subjects. Response rates were consistent across subgroups, with robust responses observed regardless of number of prior regimens, refractoriness to last prior therapy, refractoriness to bendamustine, disease subtype, bulky status, age, and gender. ORRs ranged from 47% to 80% in various subgroups. The ORR in this population of heavily pretreated refractory subjects was clinically meaningful and robust.

In subjects with FL (N = 72), the ORR (95% CI), based on the IRC assessments, was 55.6% (43.4 to 67.3; n = 40): 12 subjects (16.7%) had a BOR of CR, 28 subjects (38.9%) had a BOR of PR.

Duration of Response:
Analysis of DOR included only subjects who achieved a CR or PR (or MR for subjects with WM) (N = 72). The KM estimate of median (95% CI) DOR for subjects was 12.5 months (7.4 to 22.4) based on the IRC assessments.

Change in SPD from Baseline:
Among subjects with measurable index lesions at both baseline and postbaseline (N = 122), 110 subjects (90.2%) had decreases from baseline in SPD, as assessed by the IRC, and 71 subjects (58.2%) achieved a ≥ 50% decrease from baseline in the SPD of index lesions. The median best percent change in SPD was a decrease of 56.8%.

Time to Response:
Analysis of time to response (TTR) includes only subjects who achieved a CR or PR (or MR for subjects with WM) on-study (N = 72). Responses were rapid with a median (range) TTR of 2.0 (1.6-33.1) months, corresponding to the first time response was evaluated (Week 8).

Progression-Free Survival:
The KM estimate of median PFS (95% CI) was 11.1 months (8.3 to 14.0) with 50.3% and 34.8% of subjects progression-free at 48 weeks and 72 weeks, respectively. Progression-free survival in subjects with FL was similar; the KM estimate of median PFS (95% CI) was 11.0 months (8.0 to 14.0), and the proportion of subjects remaining progression-free at 48 weeks and 72 weeks was estimated to be 46.0% and 34.6%, respectively.

Overall Survival:
The KM estimate of median OS including long-term follow-up was 48.6 months and the proportion of subjects surviving at 48, 72, 96, and 120 weeks was estimated to be 82.5%, 70.3%, 66.7%, and 63.9%, respectively. Overall survival in subjects with FL was generally similar; the KM estimate of median OS including long-term follow-up for subjects with FL was 61.2 months and the proportion of subjects surviving at 48, 72, 96, and 120 weeks was estimated to be 88.4%, 75.1%, 70.5%, and 70.5%, respectively.

Health-Related Quality of Life:
Median subscale scores of the FACT-Lym questionnaire remained constant over time with the exception of the Additional Concerns subscale (lymphoma subscale [LymS]), specific to lymphoma symptoms, which increased, representing improvement. The median best change from baseline in the LymS subscale was 5.0, equaling the minimally important difference (MID) of 5.0. The cumulative distribution for this subscale indicated that ≥ 90% of subjects reported an improvement in their assessment of lymphoma-related symptoms at some point in the study.

Pharmacokinetics/Pharmacodynamics Results: No PK or pharmacodynamic assessments were performed for this report. Results from the PK analyses were presented in the Study 101-09 Primary Analysis CSR (12 August 2013). Pharmacodynamic analyses are ongoing and might be provided separately as an addendum.

Safety Results:

Exposure:
The median (first quartile [Q1], third quartile [Q3]) duration of exposure to IDL in the ITT Analysis Set was 6.6 (3.6, 17.6) months, with a range of 0.6 to 81.0 months. A total of 49 subjects (39.2%) had reductions in dose from the starting dose of 150 mg twice daily. Four subjects (3.2%) had their dose reduced to 75 mg twice daily. Of the 45 subjects (36.0%) who had their dose reduced to 100 mg twice daily, 6 subjects (4.8%) had their dose further reduced to 75 mg twice daily. Forty-one of the 49 subjects with dose reductions had AEs leading to these reductions.

The median (Q1, Q3) duration of exposure to IDL in the subgroup of subjects with FL was 6.5 (3.7, 13.6) months, with a range of 0.6 to 69.2 months.

Adverse Events:
AEs were consistent with those expected for a highly refractory population of subjects with iNHL and with the established safety profile of IDL. Adverse events in the ITT Analysis Set occurred in 123 subjects (98.4%). The most commonly reported AEs were diarrhea (61 subjects [48.8%]), pyrexia (41 subjects [32.8%]), and fatigue and cough (each 40 subjects [32.0%]). A total of 96 subjects (76.8%) reported at least 1 ≥ Grade 3 AE, and the most frequently reported were neutropenia (28 subjects [22.4%]), diarrhea (21 subjects [16.8%]), and pneumonia (16 subjects [12.8%]).

Adverse events in the subgroup of subjects with FL occurred in 71 subjects (98.6%). The most commonly reported AEs were diarrhea (37 subjects [51.4%]), cough (23 subjects [31.9%]), and pyrexia (22 subjects [30.6%]). A total of 49 subjects (68.1%) reported at least 1 ≥ Grade 3 AE, and the most frequently reported were neutropenia (14 subjects [19.4%]), diarrhea (10 subjects [13.9%]), and hypokalemia (7 subjects [9.7%]).

<u>Adverse Events Related to IDL</u>
The most frequently reported AEs assessed by the investigator as related to IDL were diarrhea (47 subjects [37.6%]), neutropenia (34 subjects [27.2%]), fatigue (26 subjects [20.8%]), nausea (22 subjects [17.6%]), and pyrexia (20 subjects [16.0%]). The most frequently reported ≥ Grade 3 AEs assessed by the investigator as related to IDL were neutropenia (26 subjects [20.8%]), diarrhea (17 subjects [13.6%]), increased alanine aminotransferase (ALT) (11 subjects [8.8%]), and pneumonia (11 subjects [8.8%]).

Adverse Events of Interest

AEs of interest (AEI) for IDL were any grade bowel perforation, ≥ Grade 3 diarrhea and/or colitis, any grade pneumonitis, any grade progressive multifocal leukoencephalopathy (PML), and ≥ Grade 3 rash by medical search term (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 cytomegalovirus (CMV) infection, and any grade *Pneumocystis jirovecii* pneumonia [PJP]). Gilead's ongoing pharmacovigilance and signal detection practices for Zydelig (idelalisib) prompted the addition of organizing pneumonia (OP) as of 01 September 2017. Subjects received trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of IDL treatment and continued for a period of 2 to 6 months after IDL discontinuation.

Bowel perforation:
A total of 3 subjects (2.4%) were identified with events on the MST list used to screen for bowel perforation, 2 subjects with perirectal abscess (Grade 2 and Grade 3 in severity) and 1 subject experienced rectal abscess (Grade 2 in severity); however, upon further evaluation, the events were limited to these abscesses only, without additional evidence of perforation. Therefore, no actual events of perforation were experienced by subjects in this study.

Diarrhea/colitis:
A total of 24 subjects (19.2%) had diarrhea/colitis events that were ≥ Grade 3 in severity (23 subjects with Grade 3 and 1 subject with Grade 4). Six subjects (4.8%) discontinued study drug due to ≥ Grade 3 diarrhea or colitis.

Pneumonitis:
Five subjects (4.0%) experienced pneumonitis (2 subjects with Grade 1, 2 subjects with Grade 3, and 1 subject with Grade 5). Three subjects (2.4%) discontinued study drug due to pneumonitis.

Progressive Multifocal Leukoencephalopathy:
No subjects experienced PML.

Rash:
Four subjects (3.2%) experienced rash by MST events that were Grade 3: 2 subjects experienced rash (both Grade 3 in severity), 1 subject experienced dermatitis exfoliative generalized (Grade 3 in severity), and 1 subject experienced rash pruritic (Grade 3 in severity). No subjects discontinued study drug due to rash MST terms.

Infections:
Thirty-three subjects (26.4%) had infections of ≥ Grade 3. Ten subjects (8.0%) discontinued study drug due to infections.

Febrile Neutropenia:
Five subjects (4.0%) had febrile neutropenia of ≥ Grade 3. Two subjects (1.6%) discontinued study drug due to ≥ Grade 3 febrile neutropenia.

CMV:
Two subjects (1.6%) had CMV infection (1 subject each Grade 3 and Grade 4). One subject (0.8%) discontinued study drug due to CMV.

***Pneumocystis jirovecii* Pneumonia:**
Two subjects (1.6%) had PJP of any grade (1 subject each Grade 3 and Grade 5). One subject (0.8%) discontinued study drug due to PJP, and subsequently died (event was Grade 5).

Organizing Pneumonia:
No subjects experienced OP.

Deaths:
A total of 64 (51.2%) deaths were reported during the study; 13 deaths occurred on study drug or within 30 days of the last dose of study drug. The remaining 51 deaths occurred during long-term follow-up. Three of the 13 deaths on-study and 37 of the 51 deaths during long-term follow-up were attributed to PD.

Causes of death were largely consistent with refractory iNHL and the underlying frailty, age, and prognosis of the study population, and were unchanged from the Study 101-09 Primary Analysis CSR. AEs leading to the death of more than 1 subject were pneumonia (3 subjects, 2.4%) and multiple organ dysfunction syndrome (2 subjects, 1.6%). Deaths due to AEs which were assessed by the investigator as related to study drug included cardiac arrest, PJP, acute respiratory distress syndrome, pneumonia, and pneumonitis.

Serious Adverse Events:
Consistent with an elderly population with NHL, SAEs were reported for the majority of subjects (72 subjects, 57.6%) in the ITT Analysis Set. The most frequently reported SAEs by PT were pneumonia (15 subjects, 12.0%), pyrexia (15 subjects, 12.0%), and diarrhea (11 subjects, 8.8%). IDL-related SAEs were reported for 45 subjects (36.0%) and the most common IDL-related SAEs were pneumonia (10 subjects, 8.0%), diarrhea (8 subjects, 6.4%), and pyrexia (6 subjects, 4.8%).

Serious AEs were reported for half the subjects (36 subjects, 50.0%) with FL. The most frequently reported SAEs by PT were pyrexia (8 subjects, 11.1%), pneumonia (5 subjects [6.9%]) and diarrhea (5 subjects, 6.9%).

Adverse Events Leading to Discontinuation of IDL:
A total of 35 subjects (28.0%) discontinued IDL due to an AE. The most common AEs that led to discontinuation were diarrhea (5 subjects, 4.0%) and ALT increased, aspartate aminotransferase (AST) increased, pneumonia, and pneumonitis (each 3 subjects, 2.4%).

Laboratory Evaluations of Interest:
Based on laboratory assessments, 72 subjects (57.6%) had decreased neutrophil count of any grade; 18 subjects (14.4%) had decreased neutrophil count of Grade 3 and 17 subjects (13.6%) of Grade 4.

Alanine aminotransferase elevations (all grades) occurred in 62 subjects (49.6%) with Grade 3 or 4 abnormalities observed in 16 subjects (12.8%). Aspartate aminotransferase elevations (all grades) occurred in 49 subjects (39.2%), with Grade 3 or 4 observed in 11 subjects (8.8%). Of the 11 subjects with Grade 3 or 4 AST elevations, 10 subjects also had Grade 3 or 4 ALT elevations. Study drug was reinitiated at 100 or 150 mg in 14 of the 16 subjects (11.2%) with Grade 3 or 4 transaminase elevations, and Grade 3 or 4 transaminase elevations recurred in 4 of these subjects: 3 subjects (2.4%) rechallenged with 100 mg twice daily and 0 subjects rechallenged with 150 mg twice daily. The median (minimum, maximum) time to onset and resolution of the first Grade 3 or 4 ALT or AST elevation was 6.4 (3.9, 71.0) weeks and 4.1 (1.1, 12.4) weeks, respectively.

At total of 37 subjects (51.4%) with FL had decreased neutrophil count of any grade; 16 subjects (22.2%) had decreased neutrophil count of Grade 3 and 17 subjects (13.6%) of Grade 4.

Alanine aminotransferase elevations (all grades) occurred in 36 subjects (50.0%) with FL with Grade 3 or 4 abnormalities observed in 8 subjects (11.1%). Aspartate aminotransferase elevations (all grades) occurred in 28 subjects (38.9%), with Grade 3 or 4 observed in 8 subjects (11.1%).

Clinical Laboratory Evaluations:
Hematologic abnormalities were frequent among subjects in all treatment groups. Hemoglobin concentrations and platelet counts trended upward with time.

CONCLUSIONS:

- IDL was highly effective in this refractory population with an ORR of 57.6%. Thirteen subjects achieved a CR and 58 subjects achieved a PR.
- In this highly refractory and heavily pre-treated patients, IDL achieved a clinically meaningful PFS (KM estimate of 11.1 months) and OS (KM estimate of 48.6 months) both of which further support the durability of IDL treatment.
- The ORR was consistent across all subgroups, regardless of disease subtype, number of prior regimens, refractoriness to last prior therapy, refractoriness to bendamustine, disease subtype, bulky status, age, and gender.
- With continued administration of IDL, responses were durable. The median DOR for subjects who responded was 12.5 months.
- Responses were rapid, with the majority apparent at the first response evaluation. The median TTR was 2.0 months.
- The KM estimate of median PFS among all subjects was 11.1 months, indicating potential clinical benefit in those with SD. The KM estimate for median OS was 48.6 months including long-term follow-up data.
- Lymphadenopathy improved (SPD decreased from baseline) in more than 90% of subjects.
- Over 90% of subjects reported some improvement from baseline in a lymphoma-specific subscale of the HRQOL FACT-Lymphoma questionnaire and 50% achieved the MID.
- Overall, the safety findings in this study are consistent with the current safety profile of IDL.

IDL, with its clinically meaningful ORR and substantial DOR, has the potential to provide effective and durable disease control as an oral monotherapy agent for patients with refractory iNHL.