# FINAL CLINICAL STUDY REPORT

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| **Study Title:** | An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects with Hematologic Malignancies |
| **Name of Test Drug:** | Idelalisib (IDL, Zydelig®, GS-1101) |
| **Dose and Formulation:** | 50, 100, 150, 200, or 350 mg IDL twice daily<br>150 or 300 mg IDL once daily<br>50-, 75-, or 100-mg capsules and 75-, 100-, or 150-mg tablets |
| **Indication:** | Hematologic Malignancies |
| **Sponsor:** | Gilead Sciences, Inc.<br>333 Lakeside Drive<br>Foster City, CA 94404<br>USA |
| **Study No.:** | 101-99 |
| **Phase of Development:** | Phase 1/2 |
| **IND No.:** | 101254 |
| **EudraCT No.:** | Not Applicable |
| **ClinicalTrials.gov Identifier:** | NCT01090414 |
| **Study Start Date:** | 22 March 2010 (First Subject Screened) |
| **Study End Date:** | 18 June 2018 (Last Subject Last Observation for this Report) |
| **Principal or Coordinating Investigator:** | Name: Richard R. Furman, MD<br>Affiliation: PPD |
| **Gilead Responsible Medical Monitor:** | Name: Pankaj Bhargava, MD<br>Telephone: PPD<br>Fax: PPD |
| **Report Date:** | 15 November 2018 |
| **Previous Report Date(s):** | 13 November 2017 Interim 4 CSR<br>01 November 2016 Interim 3 CSR<br>09 February 2015 Interim 2 CSR<br>30 July 2013 Interim 1 CSR |

# STUDY SYNOPSIS

**Study 101-99**
**Gilead Sciences, Inc.**
**333 Lakeside Drive**
**Foster City, CA 94404**
**USA**

**Title of Study:** An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects with Hematologic Malignancies

**Investigators:** Multicenter Study

**Study Centers:** 18 sites in the United States (US, USA)

**Publications:**

Barrientos J, Coutre SE, et al. (2014). Long-Term Follow-Up of a Phase 1 Trial of Idelalisib (ZYDELIG®) in Combination with Bendamustine, Bendamustine/Rituximab, Fludarabine, Chlorambucil, or Chlorambucil/Rituximab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) [Abstract 3343]. 56th American Society of Hematology (ASH) Annual Meeting and Exposition, San Francisco, California.

Barrientos JC, Leonard JP, et al. (2013). Update on a Phase 1 Study of the Selective PI3Kδ Inhibitor, Idelalisib (GS-1101) in Combination with Rituximab and/or Bendamustine in Patients with Relapsed or Refractory CLL [Presentation]. American Society for Clinical Oncology (ASCO) Annual Meeting, Chicago, Illinois.

Barrientos JC, Wagner-Johnston ND, et al. (2013). Chemo-Immunotherapy Combination of Idelalisib with Bendamustine/Rituximab or Chlorambucil/Rituximab in Patients with Relapsed/ Refractory CLL Demonstrates Efficacy and Tolerability [Poster 4176]. 55th ASH Annual Meeting and Exposition, New Orleans, Louisiana.

Barrientos JC, Sharman J, et al. (2012). GS-1101 (CAL-101), A Selective Phosphatidylinositol 3-Kinase-Delta Inhibitor, in Combination With Ofatumumab for the Treatment of Relapsed/ Refractory CLL [Abstract 1062]. Haematologica: the Hematology Journal 17th Congress of the European Hematology Association 14-17 June 2012 Amsterdam; Netherlands 97 (Suppl 1): 433.

Benson D, Kahl BS, et al. (2013). Final Results of a Phase 1 Study of Idelalisib, a Selective Inhibitor of PI3Kδ, in Patients with Relapsed or Refractory Indolent non-Hodgkin Lymphoma [Presentation]. ASCO Annual Meeting, Chicago, Illinois.

Brown JR, Cheson BD, et al. (2015). Patterns of Lymphocytosis in Patients with CLL or Small Lymphocytic Lymphoma (SLL) Treated with Idelalisib. 57th ASH Annual Meeting and Exposition, Orlando, Florida.

Brown JR, Byrd JC, et al. (2014). Idelalisib, an Inhibitor of Phosphatidylinositol 3 Kinase p110δ, for Relapsed/Refractory CLL. Blood, 123:22, 3390-3397.

Brown JR, Furman RR, et al. (2013). Final Results of a Phase 1 Study of Idelalisib (GS-1101) a Selective Inhibitor of Phosphatidylinositol 3-Kinase p110 Delta (PI3Kδ) in Patients with Relapsed or Refractory CLL [Presentation]. ASCO Annual Meeting, Chicago, Illinois.

Coutre S, Flinn I, et al. (2018). Idelalisib in Combination with Rituximab or Bendamustine or Both in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia. HemaSphere, 2:3.

Coutre S, Barrientos C, et al. (2015). Safety of Idelalisib in B-cell Malignancies: Integrated Analysis of Eight Clinical Trials. ASCO Annual Meeting, Chicago, Illinois.

Coutre S, Leonard J, et al. (2015). Idelalisib Monotherapy Results in Durable Responses in Patients with Relapsed or Refractory Waldenstrom's Macroglobulinemia. ASCO Annual Meeting, Chicago, Illinois.

DeVos S, Wagner-Johnston ND, et al. (2014). Durable Responses Following Treatment with the PI3K-Delta Inhibitor Idelalisib in Combination with Rituximab, Bendamustine, or Both, in Recurrent Indolent non-Hodgkin Lymphoma: Phase I/II Results [Abstract 3063]. 56th ASH Annual Meeting and Exposition, San Francisco, California.

DeVos S, Furman RR, et al. (2013). Idelalisib, a Selective Inhibitor of PI3Kδ, in Combination with Bendamustine, Fludarabine, or Chlorambucil in Patients with Relapsed or Refractory (R/R) CLL [Poster 2878]. 55th ASH Annual Meeting and Exposition, New Orleans, Louisiana.

Flinn IW, Kahl BS, et al. (2014). Idelalisib, a Selective Inhibitor of Phosphatidylinositol 3-Kinase-δ, as Therapy for Previously Treated Indolent non-Hodgkin Lymphoma. Blood, 123:22, 3406-3413.

Furman R, DeVos S, et al. (2014). Long-Term Follow-Up of a Phase 1 Study of Idelalisib (ZYDELIG®) in Combination with Anti-CD20 Antibodies (Rituximab or Ofatumumab) in Patients with Relapsed or Refractory CLL. 56th ASH Annual Meeting and Exposition, San Francisco, California.

Furman R, Sharman J, et al. (2013). A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib and Rituximab for Previously Treated Patients with CLL [Abstract LBA-6]. 55th ASH Annual Meeting and Exposition, New Orleans, Louisiana.

Ghia P, Cheson BD, et al. (2016). Patterns of Idelalisib Treatment-Emergent Lymphocytosis in Patients with CLL or SLL [poster]. EHA 21st Congress, Copenhagen, Denmark.

Ghia P, Coutre S, et al. (2016). Management of Transaminase Elevations Associated with Idelalisib [poster]. European Hematology Association (EHA) 21st Congress, Copenhagen, Denmark.

Gopal AK, Davies AJ, et al. (2015). Idelalisib Monotherapy and Durable Responses in Patients with Relapsed or Refractory SLL. 57th ASH Annual Meeting and Exposition, Orlando, Florida.

Kahl BS, Spurgeon SE, et al. (2014). Results of a Phase I Study of Idelalisib, a PI3Kδ Inhibitor, in Patients with Relapsed or Refractory Mantle Cell Lymphoma. Blood, 123:22, 3398-3405.

Leonard JP, Wagner-Johnston ND, et al. (2013). Combinations of the PI3Kδ Inhibitor Idelalisib (GS-1101) with Rituximab and/or Bendamustine are Tolerable and Highly Active in Patients with Previously Treated, Indolent non-Hodgkin Lymphoma: Updated Results from a Phase I Study [Presentation]. ASCO Annual Meeting, Chicago, Illinois.

Martin P, Armas A, et al. (2015). Idelalisib Monotherapy and Durable Responses in Patients with Relapsed or Refractory Marginal Zone Lymphoma (MZL). 57th ASH Annual Meeting and Exposition, Orlando, Florida.

O'Brien SM, Lamanna N, et al. (2015). A Phase 2 Study of Idelalisib Plus Rituximab in Treatment- Naïve Older Patients with CLL. Blood, 126:25, 2686-2694.

O'Brien SM, Lamanna N, et al. (2014). Update on a Phase 2 Study of Idelalisib in Combination with Rituximab in Treatment-Naive Patients ≥ 65 Years with CLL or SLL [Poster 1994]. 56th ASH Annual Meeting and Exposition, San Francisco, California.

O'Brien SM, Lamanna N, et al. (2013). A Phase 2 Study of the Selective Phosphatidylinositol 3-Kinase Delta (PI3Kδ) Inhibitor Idelalisib (GS-1101) in Combination with Rituximab in Treatment-Naive Patients ≥ 65 Years with CLL or SLL [Presentation]. ASCO Annual Meeting, Chicago, Illinois.

Spurgeon SE, Wagner-Johnston ND, et al. (2013). Final Results of a Phase 1 Study of Idelalisib, a Selective Inhibitor of Phosphatidylinositol 3-Kinase P110δ (PI3Kδ) in Patients with Relapsed or Refractory Mantle Cell Lymphoma [Presentation]. ASCO Annual Meeting, Chicago, Illinois.

Wagner-Johnston ND, DeVos S, et al. (2013). Preliminary Results of PI3Kδ Inhibitor Idelalisib (GS-1101) Treatment in Combination with Everolimus, Bortezomib, or Bendamustine/Rituximab in Patients with Previously Treated Mantle Cell Lymphoma [Presentation]. ASCO Annual Meeting, Chicago, Illinois.

Wierda W, Coutre S, et al. (2016). Management of Transaminase Elevations in Patients Receiving Idelalisib. ASCO Annual Meeting, Chicago, Illinois.

**Study Period:**

22 March 2010 (First Subject Screened)
18 June 2018 (Last Subject Last Observation for this Report)

**Phase of Development:** Phase 1/2

**Objectives:**

The primary objectives of this study were as follows:

- To investigate the long-term safety of idelalisib (IDL, Zydelig®, GS-1101, CAL-101) in subjects with hematologic malignancies
- To determine the duration of clinical benefit of IDL in subjects with hematologic malignancies

**Methodology:**

This was a long-term safety extension study of IDL in subjects with hematologic malignancies who completed 48 weeks of treatment with IDL in Studies 101-02, 101-07, 101-08[1], or 101-10 (ie, parent studies) and who received clinical benefit from treatment with IDL. Subjects were followed according to the standard of care appropriate for their type of cancer. The dose of IDL was the same as the dose administered at the end of the parent study. Subjects were withdrawn from the study if they developed disease progression (PD), unacceptable toxicity related to IDL, or, if in the opinion of the investigator, they no longer derived clinical benefit.

In 2017, following a review of ongoing IDL clinical development studies, Gilead determined that a number of legacy studies, including Study 101-99, had few remaining active subjects and limited additional safety data to be generated if the studies were to continue. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) agreed with Gilead's proposal to close Study 101-99 and transition remaining subjects to receive commercial Zydelig®. The study was being conducted in part to fulfill an FDA postmarketing requirement and an EMA post-authorization measure. On 18 June 2018, Gilead transitioned the last remaining subject in Study 101-99 to receive commercial Zydelig®.

**Number of Subjects (Planned and Analyzed):**

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| Planned: | There was no limit to the number of subjects |
| Analyzed: | 514 subjects enrolled in the parent studies[2]; 202 subjects subsequently enrolled in Study 101-99 |

**Diagnosis and Main Criteria for Inclusion:** Subjects with hematologic malignancies who completed a prior study of IDL with clinical benefit.

**Duration of Treatment:** Treatment continued for as long as the subject derived clinical benefit without documented PD.

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

Idelalisib doses of 50, 100, 150, 200, or 350 mg orally twice daily or 100, 150, 200, or 300 mg orally once daily, formulated as 50-, 75-, and 100-mg capsules or 75-, 100-, and 150-mg tablets.

Formulations and lot numbers administered in this study included the following:

- 50-mg IDL capsules: Lot numbers B100718, B090558, and B090201
- 75-mg IDL capsules: Lot number B090671
- 100-mg IDL capsules: Lot numbers B090298 and B090393
- 75-mg IDL tablets: Lot numbers B100653 and CV1103B1

[1] All results presented for Study 101-08 in this report include data from Cohort 1 only; subjects in Cohort 2 did not enroll in Study 101-99.
[2] Parent studies referenced in this report include Study 101-02 (subjects with chronic lymphocytic leukemia [CLL] only), Study 101-07, Study 101-08 Cohort 1, and Study 101-10.

- 100-mg IDL tablets: Lot numbers CV1102B1, CV1106B1, CV1107B2, CV1110C1, CV1205C1, CY1201B1, and PCZX
- 150-mg IDL tablets: Lot numbers CV1104D1, CV1105B1, CV1110D2, CV1107D2, CV1205D1, CV1305B1, and CV1402B1

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

**Criteria for Evaluation:**

**Efficacy:** Efficacy data from all subjects in the parent studies, regardless of subsequent participation in Study 101-99, were aggregated with data from Study 101-99, and are presented by parent study. Response was assessed using standard response criteria for each disease type. The proportion of subjects with a complete response (CR), partial response (PR), minor response (MR, evaluated only for subjects with lymphoplasmacytic lymphoma [LPL]/Waldenstrom macroglobulinemia [WM]), stable disease (SD), PD, or who were not evaluable (NE) was summarized. Overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), time to response (TTR), and overall survival (OS) were also summarized.

**Safety:** Safety data are presented as follows:

- Safety data from all subjects in the parent studies, regardless of subsequent participation in Study 101-99, were aggregated with data from Study 101-99, and are presented by parent study.
- Safety data from the parent studies for the subset of subjects who enrolled in Study 101-99 were aggregated with data from Study 101-99, and are presented by parent study.
- Safety data reported during Study 101-99 only.

All adverse events (AEs) presented in this report were treatment emergent and are referred to as AEs in this report. Safety was evaluated by assessing all Grade 3 or higher AEs and all serious adverse events (SAEs). The severity of AEs was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) versions 3.0, 4.02, or 4.03, depending upon the protocol version being used when the AE was reported.

**Statistical Methods:**

Subjects with the following disease types enrolled in the parent studies: Chronic lymphocytic leukemia (CLL, N = 228), indolent non-Hodgkin lymphoma (iNHL, N = 168[3]), small lymphocytic lymphoma (SLL, N = 5), mantle cell lymphoma (MCL, N = 80), acute myeloid leukemia (AML, N = 12), diffuse large B-cell lymphoma (DLBCL, N = 9), and multiple myeloma (N = 12), for a total of 514 subjects. No subjects with AML, DLBCL, or multiple myeloma completed 48 weeks of therapy with IDL in the parent study; therefore, none were eligible for enrollment in Study 101-99.

**Efficacy:** Efficacy data from all subjects in the parent studies (regardless of subsequent participation in Study 101-99) were aggregated with data from Study 101-99, and are presented by parent study and disease type. The 2013 National Comprehensive Cancer Network (NCCN) response criteria were used to assess response.

[3] Sixty-four subjects categorized with iNHL in Study 101-02 included 38 subjects with follicular lymphoma (FL), 11 subjects with SLL, 9 subjects with LPL/WM, and 6 subjects with marginal zone lymphoma (MZL).

Efficacy results were analyzed as follows:

- Overall response rate: Defined as the proportion of subjects who achieved a CR, PR, or MR at any time between initiation of IDL treatment and End of Study or PD, whichever occurred first
- Duration of response: Defined as the interval (in months) from the first documentation of CR, PR, or MR to the earlier of the first documentation of PD or death from any cause. For surviving and non-PD subjects, data was censored on the date of the last tumor assessment for DOR calculations. DOR was only evaluated for subjects who had a response of CR, PR, or MR.
- Progression-free survival: Defined as the interval (in months) from the start of IDL treatment on the parent study to the earlier of the first documentation of PD or death from any cause. For surviving and non-PD subjects, data was censored on the date of the last tumor assessment
- Time to response: Defined as the interval from the start of IDL treatment on the parent study to the first documentation of CR, PR, or MR. TTR was only evaluated for subjects who had a response of CR, PR, or MR
- Overall survival: Defined as the interval from the start of study treatment to death from any cause

**Safety:** Safety results are summarized as follows:

- Cumulative safety data reported for all subjects during the parent study and Study 101-99, regardless of subsequent participation in Study 101-99
- Cumulative safety data reported for the subset of subjects who enrolled in Study 101-99, during the parent study and Study 101-99
- Safety data reported during Study 101-99 only

The Intent To Treat (ITT) Analysis Set included all subjects who received ≥ 1 dose of IDL. This analysis set was used for all efficacy and safety analyses. Adverse events were classified by system organ class (SOC), high-level group term, high level term (HLT), preferred term (PT), and lower level term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0. An overview of AEs, which includes the incidence of AEs ≥ Grade 3, IDL-related AEs ≥ Grade 3, AEs leading to study discontinuation, SAEs, IDL-related SAEs, and deaths is presented. In addition, tabular summaries of AEs, IDL-related AEs, AEs ≥ Grade 3, SAEs, AEs leading to IDL discontinuation, AEs of interest (AEIs), AEs leading to death, and deaths are presented. Listings of AEs that occurred during Study 101-99 are provided.

**SUMMARY OF RESULTS:**

**Subject Disposition and Demographics:**

Most subjects who completed a parent study (212 of 514 subjects, 41.2%) enrolled in Study 101-99 (202 of 212 subjects, 95.3%). The database finalization date for Study 101-99 was 18 September 2018.

Study 101-99 is complete. All subjects received at least 1 dose of IDL, and all subjects have discontinued the study. The most common reason for study discontinuation was PD (90 subjects, 44.6%).

Of the subjects from parent Study 101-02 who enrolled in Study 101-99 (N = 48), 79.2% were male and 20.8% were female. Most subjects were white (89.6%). Data regarding Latino or Hispanic ethnicity was not collected. The mean (StD) age at enrollment in the parent study was 64 (11.0) years (range: 32 to 83 years). The division of subjects by age category was approximately even: 47.9% were < 65 years of age and 52.1% were ≥ 65 years of age. Upon enrollment in the parent study, nearly all subjects had a WHO performance status of 0 or 1 (41.7% and 56.3%, respectively). The majority of subjects, 66.7%, had bulky adenopathy.

Of the subjects from parent Study 101-07 who enrolled in Study 101-99 (N = 108), 66.7% were male and 33.3% were female. Most subjects were white (88.0%) and of non-Hispanic/Latino ethnicity (97.2%). The mean (StD) age at enrollment in the parent study was 63 (9.9) years (range: 37 to 86 years). The majority of subjects, 58.3%, were < 65 years of age, 41.7% were ≥ 65 years of age. Upon enrollment in the parent study, all subjects had a WHO performance status of 0 or 1 (67.3% and 32.7%, respectively). The majority of subjects, 60.2%, had bulky adenopathy.

Of the subjects from parent Study 101-08 who enrolled in Study 101-99 (N = 41), 61.0% were male and 39.0% were female. Most subjects were white (92.7%), and all subjects (100%) were of non-Hispanic/Latino ethnicity. The mean (StD) age at enrollment in the parent study was 71 (5.3) years (range: 65 to 86 years). All subjects (100%) were ≥ 65 years of age. Upon enrollment in the parent study, most subjects had a WHO performance status of 0 or 1 (51.2% and 46.3%, respectively). Only 14.6% of subjects had bulky adenopathy.

Of the subjects from parent Study 101-10 who enrolled in Study 101-99 (N = 5), 40.0% were male and 60.0% were female. Most subjects were white (80.0%) and of non-Hispanic/Latino ethnicity (80.0%). The mean (StD) age at enrollment in the parent study was 60 (6.3) years: (range: 51 to 67 years). The majority of subjects (80.0%) were < 65 years of age. Upon enrollment in the parent study, all subjects had a WHO performance status of 0 or 1 (60.0% and 40.0%, respectively), and no subject (0%) had bulky adenopathy.

**Efficacy Results:**

Efficacy data from all subjects in the parent studies (regardless of subsequent participation in Study 101-99) are aggregated with data from Study 101-99. Results for subjects with iNHL, MCL, FL, SLL, LPL/WM, and MZL from Study 101-02 are not presented in this CSR because there have been no new data since they were summarized in the Study 101-99 Interim 2 CSR. The results summarized below are consistent with those reported from earlier analyses of this study.

Overall Response Rate

Among subjects with CLL, the ORR (95% CI) for relapsed/refractory subjects treated with IDL monotherapy (Study 101-02, N = 54) based on the 2013 NCCN response criteria was 72.2% (58.4%, 83.5%); the ORR (95% CI) for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 115) was 81.7% (73.5%, 88.3%); and the ORR (95% CI) for previously untreated subjects treated with IDL combination therapy (Study 101-08, N = 64) was 96.9% (89.2%, 99.6%).

Among subjects with iNHL, the ORR (95% CI) for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 86) was 82.6% (72.9%, 89.9%), and the ORR (95% CI) for previously treated subjects treated with IDL monotherapy (Study 101-10, N = 18) was 44.4% (21.5%, 69.2%).

Among subjects with MCL, the ORR (95% CI) for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 40) was 57.5% (40.9%, 73.0%).

Overall, 19 of 177 subjects (10.7%) who entered Study 101-99 (subjects with CLL from Study 101-02 and subjects from Studies 101-07, 101-08, and 101-10) had an improved response during Study 101-99: 4 subjects improved from SD to PR (1 subject with CLL and 3 subjects with iNHL), and 15 subjects improved from PR to CR (10 subjects with CLL, 4 subjects with iNHL, and 1 subject with MCL).

Duration of Response

Among subjects with CLL, the KM estimate (95% CI) of median DOR for relapsed/refractory subjects treated with IDL monotherapy (Study 101-02, N = 54) based on the 2013 NCCN response criteria was 16.2 (4.6, 32.8) months; the KM estimate (95% CI) of median DOR for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 115) was 26.6 (18.5, 44.1) months; and the KM estimate (95% CI) of median DOR for previously untreated subjects treated with IDL combination therapy (Study 101-08, N = 64) was 63.8 (54.0, NE) months.

Among subjects with iNHL, the KM estimate (95% CI) of median DOR for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 86) was 42.9 (20.5, 83.3) months. The KM estimate (95% CI) of median DOR for previously treated subjects treated with IDL monotherapy (Study 101-10, N = 18) was 14.4 (6.6, 46.3) months.

Among subjects with MCL, the KM estimate (95% CI) of median DOR for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 40) was 9.3 (5.6, 37.5) months.

Progression-Free Survival

Among subjects with CLL, the KM estimate (95% CI) of median PFS for relapsed/refractory subjects treated with IDL monotherapy (Study 101-02, N = 54) was 15.8 (5.6, 39.6) months; the KM estimate (95% CI) of median PFS for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 115) was 26.1 (19.0, 36.8) months; and the KM estimate of median PFS for previously untreated subjects treated with IDL combination therapy (Study 101-08, N = 64) was 65.6 (55.8, NE) months.

Among subjects with iNHL, the KM estimate (95% CI) of median PFS for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 86) was 32.8 (22.0, 81.3) months and the KM estimate (95% CI) of median PFS for previously treated subjects treated with IDL monotherapy (Study 101-10, N = 18) was 10.2 (2.8, 19.1) months.

Among subjects with MCL, the KM estimate (95% CI) of median PFS for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 40) was 11.1 (3.4, 12.9) months.

Time to Response

Among subjects with CLL, the median (Q1, Q3) TTR for relapsed/refractory subjects treated with IDL monotherapy (Study 101-02, N = 54) based on the 2013 NCCN criteria was 1.0 (1.0, 1.9) months; the median (Q1, Q3) TTR for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 115) was 1.9 (1.9, 1.9) months; and the median (Q1, Q3) TTR for previously untreated subjects with CLL who received IDL combination therapy (Study 101-08, N = 64) was 1.9 (1.9, 1.9) months.

Among subjects with iNHL, the median (Q1, Q3) TTR for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 86) was 1.9 (1.9, 3.0) months, and the median (Q1, Q3) TTR for previously treated subjects treated with IDL monotherapy (Study 101-10, N = 18) was 2.7 (2.6, 3.1) months.

Among subjects with MCL, the median (Q1, Q3) TTR for relapsed/refractory subjects treated with IDL combination therapy (Study 101-07, N = 40) was 1.9 (1.9, 2.0) months.

Overall Survival

The KM estimate of median OS was not reached for any disease type (CLL, iNHL, or MCL) or treatment type (monotherapy or combination therapy). The estimated proportion of subjects surviving at 84 months ranged from 57.0% (among subjects with CLL treated with IDL combination therapy on Study 101-02) to 85.0% (among subjects with iNHL treated with IDL combination therapy on Study 101-07).

**Pharmacokinetics/Pharmacodynamics Results:** No pharmacokinetic or pharmacodynamic evaluations were conducted for this study.

**Safety Results:** Per the original study protocol, only AEs ≥ Grade 3 in severity were to be collected during Study 101-99. However, beginning with protocol Amendment 5, AEs of any grade were collected. Safety was evaluated by assessing all Grade 3 or higher AEs and all SAEs. The incidence of AEs ≥ Grade 3 was 84.2% (433 of 514 subjects) for the parent studies and extension study combined, 87.1% (176 of 202 subjects) for the parent and extension study combined among the subset of subjects who enrolled in the extension study, and 67.3% (136 of 202 subjects) for the extension study alone.

Parent Study 101-02

Overall, 191 subjects enrolled in Study 101-02, of which 146 subjects (76.4%) reported at least 1 AE ≥ Grade 3 during their participation in Studies 101-02 and/or 101-99. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in either study included the following: pneumonia (31 subjects, 16.2%), neutropenia (24 subjects, 12.6%), and ALT increased (23 subjects, 12.0%). Only subjects with CLL had new data following the Study 101-99 Interim 2 CSR; therefore, only data for subjects with CLL are included in this report.

Among the subset of subjects from Study 101-02 who enrolled in Study 101-99 (N = 48), 40 subjects (83.3%) reported at least 1 AE ≥ Grade 3 during their participation in either study. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in either study included the following: pneumonia (12 subjects, 25.0%), diarrhea and neutropenia (10 subjects each, 20.8%), colitis and thrombocytopenia (6 subjects each, 12.5%), and anemia (5 subjects, 10.4%).

Among the same subset of subjects, 30 subjects (62.5%) reported at least 1 AE ≥ Grade 3 during their participation in Study 101-99 only. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in Study 101-99 included the following: pneumonia (8 subjects, 16.7%), and colitis and diarrhea (6 subjects each, 12.5%).

Parent Study 101-07

Overall, 241 subjects enrolled in Study 101-07, of which 217 subjects (90.0%) reported at least 1 AE ≥ Grade 3 during their participation in Studies 101-07 and/or 101-99. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in either study included the following: neutropenia (85 subjects, 35.3%), pneumonia (41 subjects, 17.0%), ALT increased (37 subjects, 15.4%), diarrhea and thrombocytopenia (34 subjects, 14.1%), and febrile neutropenia (28 subjects, 11.6%).

Among the subset of subjects from Study 101-07 who subsequently enrolled in Study 101-99 (N = 108), 97 subjects (89.8%) reported at least 1 AE ≥ Grade 3 during their participation in Studies 101-07 and/or 101-99. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in either study included the following: neutropenia (48 subjects, 44.4%), pneumonia (28 subjects, 25.9%), ALT increased (20 subjects, 18.5%), diarrhea (19 subjects, 17.6%), AST increased and febrile neutropenia (14 subjects each, 13.0%).

Of this same subset of subjects, 73 subjects (67.6%) reported at least 1 AE ≥ Grade 3 during their participation in Study 101-99. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in Study 101-99 included the following: pneumonia (21 subjects, 19.4%), diarrhea (15 subjects, 13.9%), and neutropenia (12 subjects, 11.1%).

Parent Study 101-08

Overall, 64 subjects enrolled in Study 101-08, of which 59 subjects (92.2%) reported at least 1 AE ≥ Grade 3 during participation in Studies 101-08 and/or 101-99. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in either study included the following: diarrhea (20 subjects, 31.3%), colitis (16 subjects, 25.0%), ALT increased (15 subjects, 23.4%), pneumonia (13 subjects, 20.3%), AST increased (12 subjects, 18.8%), and transaminases increased (7 subjects, 10.9%).

Among the subset of subjects from Study 101-08 who subsequently enrolled in Study 101-99 (N = 41), 37 subjects (90.2%) reported at least 1 AE ≥ Grade 3 during their participation in either study. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in either study included the following: colitis and diarrhea (13 subjects each, 31.7%), ALT increased and pneumonia (8 subjects each, 19.5%), and AST increased and transaminases increased (6 subjects each, 14.6%).

Of this same subset of subjects, 32 subjects (78.0%) reported AEs ≥ Grade 3 during their participation in Study 101-99. AEs ≥ Grade 3 reported for ≥ 10% of subjects during participation in Study 101-99 included the following: diarrhea (10 subjects, 24.4%), colitis (8 subjects, 19.5%) and pneumonia (6 subjects, 14.6%).

Parent Study 101-10

Overall, 18 subjects enrolled in Study 101-10, of which 11 subjects (61.1%) reported at least 1 AE ≥ Grade 3 during their participation in Studies 101-10 and/or 101-99. Among the subset of subjects from Study 101-10 who enrolled in Study 101-99 (N = 5), 2 subjects (40.0%) reported at least 1 AE ≥ Grade 3 during their participation in either study and 1 subject (20.0%) reported AEs ≥ Grade 3 during participation in Study 101-99.

Deaths

Overall, AEs leading to death have been reported for 47 of 514 subjects (9.1%) during the parent study or Study 101-99: 12 subjects (6.3%) from parent Study 101-02, 28 subjects (11.6%) from parent Study 101-07, 5 subjects (7.8%) from parent Study 101-08, and 2 subjects (11.1%) from parent Study 101-10. Adverse events leading to death reported for ≥ 2 subjects included the following: sepsis (8 subjects, 1.6%); pneumonia (7 subjects, 1.4%); respiratory failure (4 subjects, 0.8%); cardiac arrest and multiple organ dysfunction syndrome (3 subjects each, 0.6%); and acute kidney injury, gastrointestinal hemorrhage, PJP, pneumonia fungal, pneumonitis, and tumor lysis syndrome (2 subjects each, 0.4%).

Among subjects who enrolled in Study 101-99 (N = 202), AEs leading to death during study 101-99 have been reported for 14 subjects (6.9%). AEs leading to death reported for ≥ 2 subjects included the following: sepsis (5 subjects, 2.5%) and pneumonia (2 subjects, 1.0%). In addition, 2 subjects died due to non-treatment emergent AEs (2 of 202 subjects, 1.0%), and 2 subjects died due to disease progression (2 of 202 subjects, 1.0%) for a total of 18 deaths during Study 101-99 (18 of 202 subjects, 8.9%.

Serious Adverse Events

Of the 514 subjects enrolled in the parent studies, SAEs have been reported for 316 subjects (61.5%) during their participation in the parent study and/or Study 101-99. SAEs reported for ≥ 5% of subjects overall included the following: pneumonia (83 subjects, 16.1%), pyrexia (40 subjects, 7.8%), febrile neutropenia (38 subjects, 7.4%), diarrhea (36 subjects, 7.0%), and colitis (35 subjects, 6.8%).

Among the subset of subjects who enrolled in Study 101-99 (N = 202), SAEs have been reported for 142 subjects (70.3%) during their participation in the parent study and/or Study 101-99. SAEs reported for ≥ 5% of subjects overall included the following: pneumonia (49 subjects, 24.3%), colitis (24 subjects, 11.9%), diarrhea and pyrexia (19 subjects each, 9.4%), febrile neutropenia (16 subjects, 7.9%), and sepsis (15 subjects, 7.4%).

Among the same subset of subjects, SAEs were reported for 118 subjects (58.4%) during their participation in Study 101-99. SAEs reported for ≥ 5% of subjects during Study 101-99 included the following: pneumonia (37 subjects, 18.3%), colitis (19 subjects, 9.4%), and diarrhea (14 subjects, 6.9%).

Discontinuations Due to Adverse Events

Overall, 66 of 202 subjects (32.7%) discontinued Study 101-99 due to an AE. AEs resulting in discontinuation reported for ≥ 5% of subjects included the following: diarrhea (21 subjects, 10.4%) and colitis (10 subjects, 5.0%).

**CONCLUSIONS:** This extension study provides evidence of the durable activity of IDL when used as a continued oral regimen subsequent to combination use with other agents. Durable responses were observed both in heavily pretreated subjects with relapsed/refractory disease and in subjects with previously untreated CLL.

Idelalisib was generally well tolerated in this extension study and the long-term safety profile is consistent with previous reports from Study 101-99 and also from that observed in the shorter-term parent studies. SAEs and AEs ≥ Grade 3 observed with continued IDL use were similar to

those observed in the parent studies, and were consistent with those expected in the relapsed, refractory population of heavily pretreated subjects who comprised the majority of this study population.

- The ORR by disease type was as follows:
  - CLL: The ORR was 72.2% for relapsed/refractory subjects treated with IDL monotherapy, 81.7% for relapsed/refractory subjects treated with IDL combination therapy, and 96.9% for treatment naive subjects treated with IDL combination therapy.
  - iNHL: The ORR was 44.4% for previously treated subjects treated with IDL monotherapy and 82.6% for relapsed/refractory subjects treated with IDL combination therapy.
  - MCL: The ORR was 57.5% for relapsed/refractory subjects treated with IDL combination therapy.
- Following combination therapy with either anti-CD20 monoclonal antibodies or chemotherapeutic agents, subjects who received continued administration of IDL had durable responses with substantial disease control continuing ≥ 5 years in some subjects.
  - CLL: The KM estimate of median DOR was 16.2 months and 26.6 months, respectively, for subjects with relapsed/refractory CLL treated with IDL monotherapy and IDL combination therapy. Median DOR was 63.8 months for treatment naive subjects treated with IDL combination therapy.
  - iNHL: The KM estimate of median DOR was 14.4 months and 42.9 months, respectively, for subjects with iNHL treated with IDL monotherapy and IDL combination therapy.
  - MCL: The KM estimate of median DOR was 9.3 months for subjects with MCL treated with IDL combination therapy.

Nineteen of 177 subjects (10.7%) had an improved response during Study 101-99 compared with the parent study.