CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	206545
Drug Name:	Idelalisib (GS-1101) 150 mg Tablet, BID
Indication(s):	Treatment of patients with chronic lymphocytic leukemia
Applicant:	Gilead Sciences, Inc.
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Keywords:

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

The applicant submitted Study GS-US-312-0116 results to seek a first-line indication for the treatment of patients who were previously treated for chronic lymphocytic leukemia. The study is designed with progression free survival as the primary endpoint and the secondary endpoints in the order of objective response rate, lymph node response rate and overall survival. Two formal interim analyses were conducted with data cutoff date on 30 August 2013 and 9 October 2013.

Based on study GS-US-312-0116, the results demonstrated statistically significant improvement based on the progression free survival in favor of the Idelalisib + rituximab treatment compared to placebo +rituximab. The p-value for the primary endpoint, progression free survival, based on the first interim analysis results crossed the pre-specified alpha boundary of 0.001 and hence a decision was made to stop the blinded-phase of the study after the first interim. A second analysis of the blinded-phase was performed based on a data cut-off date of 9 October 2013. The median PFS time was not reached [95% CI= (10.7, NR)] in the Idelalisib + rituximab arm whereas its 5.5 months [95% CI= (3.8, 7.1)] in the placebo +rituximab arm and the hazard ratio estimate was 0.18[95% CI= (0.10, 0.32); p-value <0.0001]. The favorable results from the Idelalisib + rituximab arm were robust based on various sensitivity analyses and consistent results were shown across different demographic and baseline disease characteristic subgroups. The result based on the objective response rate [ORR=74.5% vs. 14.5% for Idelalisib + rituximab and placebo +rituximab arm, respectively; p-value <0.0001] and the lymph node response [LNR=85.5% vs. 5.5% for Idelalisib + rituximab and placebo +rituximab arm, respectively; p-value <0.0001] also demonstrated statistical significance in favor of the Idelalisib + rituximab arm. However, overall survival results were dubious because the number of events is too small to draw conclusions (19 total events). The significance level for interim analysis of overall survival was not specified in the protocol, nor the analysis was powered for overall survival. The second interim data was too premature to allow adequate conclusion about overall survival.

In conclusion, this statistical reviewer confirms the applicant's efficacy results submitted. Whether the dubious results demonstrate an overall favorable benefit to risk ratio in supporting an indication of the Idelalisib +rituximab treatment in patients with previously treated chronic lymphocytic leukemia will be deferred to the clinical review team.

2 INTRODUCTION

This following section will provide information on the drug development for this submission, the studies submitted, and those selected for the review.

2.1 Overview

The applicant submitted a study package containing studies, GS-US-312-0116 and GS-US-312-0117. Study GS-US-312-0116 is a Phase 3, randomized, double-blind study designed to evaluate the efficacy and safety of Idelalisib in combination with rituximab compared with placebo + rituximab in previously treated subjects with CLL. Study GS-US-312-0117 is a separate, multicenter, 2-group, double-blind, extension study that is a companion study to the primary study (GS-US-312-0116). Subjects who developed definitive disease progression in the primary study (GS-US-312-0116) were eligible for enrollment in a separate, companion extension study (GS-US-312-0117). In the extension study subjects took Idelalisib + rituximab therapy, either at a higher dose or at the standard dose, with allocation based on the original primary study randomization. The submission is to support the indication for Idelalisib in combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) who (b) (4)

Study GS-US-312-0116 included 2 pre-specified formal interim efficacy analyses and this review provides a summary of the clinical efficacy and statistical issues for the second interim data analysis along with a summary of the results of the first interim analysis.

The primary efficacy endpoint of the study GS-US-312-0116 was progression free survival (PFS). The secondary efficacy endpoints included overall response rate (ORR), lymph node response (LNR), overall survival (OS) and complete response rate (CR). However, no formal analysis on CR was performed because there were no CR events. The first subject was randomized on 01 May 2012 and the last subject was randomized on 28 August 2013. This was a multi-center study with a total of 58 sites in the US, France, UK, Italy and Germany.

Subjects were randomized 1:1 to receive first dose of rituximab at 375 mg/m^2 on Day 1 (Week 0); thereafter at 500 mg/m^2 intravenously on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16) and Day 141 (Week 20) for a total of 8 infusions in combination with either an oral placebo twice daily or with Idelalisib 150 mg taken twice daily until disease progression or unacceptable toxicity. Idelalisib will be referred as Idela throughout this statistical review.

Some key information for the supporting study is summarized in the following table:

Table 1: List of all studies included in analysis

Applicant defined study number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
GS-US-312-0116	*Phase 3, Randomized, Double-Blind, Placebo-Controlled*	*Study drug (Idela/placebo) will be taken continuously until the earliest of subject withdrawal from study drug, definitive progression of CLL, intolerable study drug-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation.* *Rituximab will be administered until the earliest of a maximum of 8 infusions, or any of the above stated reasons for the study drug.*	*Minimum of 12 months of follow-up period.* *The median follow-up time : Idela + rituximab: 5.5 months; Placebo + rituximab : 4.6 months*	*Treatment Arm: Idela + rituximab: 110* *Control Arm: Placebo + rituximab:110*	*e.g., Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy, require therapy for CLL, have experienced CLL progression <24 months since the completion of the last prior therapy, and are currently not sufficiently fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities*

2.2 Data Sources

The application's data (including raw and analysis datasets) from the original submission for the first and second interim for study GS-US-312-0116 is located in the following links respectively:

\\CDSESUB1\evsprod\NDA205858\0006\m5\datasets\gs-us-312-0116
\\CDSESUB1\evsprod\NDA205858\0009\m5\datasets\gs-us-312-0116

The SAS programs that were used to derive the analysis datasets and perform the analysis were also included in the link shown above.

The clinical study reports and the statistical analysis plan for this study are located in the following link:

\\CDSESUB1\evsprod\NDA205858\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\fl-sll-lpl-mzl\5351-stud-rep-contr\gs-us-312-0116

3 STATISTICAL EVALUATION

Summary of Protocol amendments:

The original protocol was finalized on 18 November 2011 and subsequently has undergone 4 amendments. Several amendments that may affect the efficacy evaluations are listed below:

Amendment 1 (23 January 2012) consisted of major clinical related modifications.

Amendment 2 (19 December 2012)

- Updated information regarding secondary and tertiary endpoints.
- Clarified that the independent review committee (IRC) findings would be considered primary for analyses of PFS and other disease control endpoints.
- Updated statistical plan to control Type I error rate for secondary endpoints.
- Modified protocol to include "death" as an event within planned sample size.
- Added new section to differentiate discontinuation from study versus discontinuation of study drug.
- Modified protocol from full analysis to intent-to-treat (ITT) analysis.
- Added the per-protocol (PP) analysis set, consistent with other sections of the protocol

Amendment 3 (21 June 2013)

- Increased planned sample size from 160 to 200 subjects in order to maintain the planned study duration. Blinded data review indicated that the actual enrollment rate was below the initial projection and the event accrual might also be slower than the initial assumptions. However, the number of PFS events remained unchanged even after the sample size increase.
- Added 2 formal interim efficacy analyses after ~50% and ~75% of the expected number of 119 PFS events (PD or deaths) had occurred.
- Added "significant subject noncompliance" and "initiation of another anticancer therapy" as reasons for study withdrawal.

Amendment 4 (10 September 2013)

- Updated disease response criteria to align with revised IRC Charter.

- Changed the order of the secondary endpoints, placing overall survival (OS) prior to complete response (CR). Based on the results of other studies in relapsed CLL with IDELA, it was expected that CR would be infrequent in this population and testing for a statistically significant difference might be less informative than OS.

Summary of SAP amendments:

The final version statistical analysis plan was signed off on 7 November 2013 and the following table reflects the amendment history of the SAP.

Table 2: Summary of SAP amendments

Revision Date	Section	Summary of Revision
5 September 2013	3.5 and 6.4	Change the order of secondary endpoint CR rate and OS
	5.2	Add in additional analyses for CIRS
	9.0	Add pharmacodynamics analysis
31 October 2013	2.1	Add conclusions from 1st interim
	6.4.2.1	Add ORR analysis by evaluable analysis set
	6.4.2.3	Add OS analysis to incorporate data from Study GS-US-312-0117
	6.2.4	Delete some PRO analysis
	7	Adding exposure-adjusted and by-time-internal AE analyses

Reviewer's comments:
The following dates submitted by the applicant summarize key dates associated with the unblinding for the first and second interim clinical study reports for Study GS-US-312-0116.

Table 3: Applicant's summary of key data cut-off and unblinding dates

	Interim-1	***Interim-2***
Data-cutoff Date	*30 August 2013*	*09 October 2013*
DMC Meeting	*22-23 September 2013*	*N/A*
Unblinding of Executive Team(1 Statistician and 1Medical writer)	*23 September 2013*	*N/A*
FDA Meeting	*07 October 2013*	*N/A*
Unblinding Date	*08 October 2013*[b]	*08 November 2013*

- *From the above dates, it was noted that applicant changed the order of secondary endpoint testing (from ORR, LNR, CR rate and OS to OR, LNR, OS and CR rate) on 9/10/2013 at the amendment #4 of the protocol and on 9/5/2013 for the SAP, after the database cutoff date for the first interim analysis (8/30/2013) but before the potential unblinding date on 9/23/2013 (unblinding the executive team including 1 statistician and 1 medical writer).*

- *Because the data was unblinded on 9/23/2013 to the executive team (including 1 medical writer and 1 statistician) and on 10/8/2013 for the first interim analysis, any revision of the analysis plan after these days will not be considered as a basis for this statistical review.*

3.1 Data and Analysis Quality

The applicant submitted raw datasets in SDTM (Study Data Tabulation Model) and analysis data sets in ADaM (Analysis Data Model Implementation) formats, the defined files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The documentation for the derived variables appears to be easy to follow. The reviewer was able to duplicate the analysis results based on the SDTM dataset as well as based on the ADaM datasets.

3.2 Evaluation of Efficacy

Study GS-US-312-0116 was a phase 3, randomized, double-blind, placebo-controlled Study evaluating the efficacy and safety of Idela in combination with rituximab for previously treated chronic lymphocytic leukemia.

The target population for this study was adults (≥18 years) who were previously treated for CLL comprising any of the following treatments:

a. Prior treatment with ≥1 regimen containing a therapeutic anti-CD20 antibody (eg, rituximab, ofatumumab, GA-101) administered for ≥2 doses of antibody treatment, or
b. Prior treatment with ≥2 regimens containing ≥1 cytotoxic agent (eg, fludarabine, pentostatin, cladribine, cyclophosphamide, chlorambucil, bendamustine) administered for ≥2 cycles of cytotoxic treatment

For a subject whose last prior therapy contained an anti-CD20 antibody, evidence of disease improvement during that therapy or documentation of CLL progression ≥6 months after completion of that therapy was required to be included in the trial. Also, for subjects who did not receive a therapeutic anti-CD20 antibody as a component of the last prior therapy need not have experienced disease improvement or may have relapsed <6 months from the completion of the prior regimen. It is required that the subject should have documentation of CLL progression <24

months since the completion of the last prior therapy for CLL. However, all therapies (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) are discontinued for the treatment of CLL ≥3 weeks before randomization.

3.2.1 Study Design and Endpoints

Eligible patients after screening were randomized in a 1:1 ratio to either the treatment arm (Idela + rituximab) or the control arm (Placebo + rituximab) and randomization was stratified using the following factors:

- 17p deletion and/or p *TP53* mutation in CLL cells: either versus neither (or indeterminate)
- Immunoglobulin heavy chain variable region (*IGHV*) mutation: unmutated (or *IGHV*3-21) versus mutated (or indeterminate)
- Any prior therapy with an anti-CD20 therapeutic antibody: yes versus no

This was a multi-center study with a total of 58 sites in the US, France, UK, Italy and Germany with 34, 7, 23, 3 and 6 investigators respectively from each country.

Primary Efficacy Endpoint:

Progression free survival: PFS, defined as the interval from randomization to the first documentation of definitive PD or death from any cause, is the primary efficacy end point.

Secondary Efficacy Endpoints:

Overall Response Rate(ORR): ORR was defined as the proportion of subjects who achieved a CR or PR during the study.

Lymph Node Response Rate: LNR is defined as the proportion of subjects who achieved ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes.

Overall Survival: OS is defined as the interval from randomization to death from any cause.

Complete Response Rate: CRR is defined as the proportion of subjects who achieve a CR.

The primary endpoint analysis will serve as the gatekeeper for the secondary endpoint analyses (in an order of ORR, LNR and OS), i.e., the primary efficacy hypothesis must be rejected at the

2-sided 0.05 significance level before the efficacy hypotheses for the secondary efficacy endpoints can be evaluated.

The determination of CLL response and progression was based on standardized international workshop on chronic lymphocytic leukemia (IWCLL) criteria. The findings of the IRC were considered primary for analyses of PFS and other disease control endpoints.

Reviewer's comment:
In the original version of the protocol, complete response was defined to have the CR criteria to persist for atleast 8 weeks. However, as per Amendment-2(19 December 2012), the information regarding the CR was updated to only having the criteria being satisfied for CR and a confirmed response after atleast 8 weeks was excluded from the assessment criteria. Hence, the ORR outcomes being analyzed in this study were not the confirmed responses.

Sample Size Calculation:

A total of 220 patients were planned to be randomized to either of the treatment arms(110 patients to each treatment arm) to achieve an improvement in median PFS from 6 months to 10.5 months due to the addition of Idela to rituximab in the treatment arm. 119 events (definitive CLL progressions) are required to detect a hazard ratio of 0.57 along with achieving a power of >0.85 based on a stratified log-rank test with a 2-sided significance level of 0.05. A planned accrual period of 12 months and a minimum follow-up period of 12 months was assumed with a 10% lost to follow-up (5% during the accrual period and 5% during the follow-up period).

Interim Analyses:

Two formal interim analyses of efficacy were planned to assess the evidence of clinical benefit. These interim analyses are conducted after ~50% and ~75% of the expected total number of PFS events (PD or deaths) had occurred. Stopping the study for substantial evidence of Idela benefit will be considered if the PFS is significantly better in the treatment arm (Idela + rituximab) compared to the control arm (placebo + rituximab). The significance level for the first interim analysis will be 0.001 and for the second interim analysis will be 0.005. If a decision is made to stop the trial based on an interim analysis, the database will be cleaned and locked for the subsequent final analysis and the significance level of 0.044 will be used.

Analysis Sets

The following analysis sets were used to perform the analysis for each end point.

Intent-to-Treat Analysis Set:

The intent-to-treat (ITT) analysis set included all subjects who were randomized regardless of whether subjects received any study drug(s), or received a different regimen from the regimen they were randomized to. Subjects in the ITT analysis set who did not

have sufficient baseline or on-study tumor status information to be adequately assessed for response status were included in the denominators in the calculation of ORR and CR rate.

Per-Protocol Analysis Set:

The per-protocol (PP) analysis set included subjects in the ITT analysis set who met the general criteria defining the target population for this study, were adherent to the protocol, were compliant with study drug treatment, and were evaluable for relevant efficacy endpoints.

Safety Analysis Set:

The safety analysis set included data from subjects who received ≥1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

The first subject was randomized on 01 May 2012 and the last subject was randomized on 28 August 2013. The clinical cutoff date for the first interim analysis was 30 August 2013 and for the second interim analysis was 09 October 2013 and all clinical data collected up to the cutoff date will be used for the interim analysis.

There were 110 patients each in treatment and control arms based on the intent-to-treat population. Two patients who were randomized to the control arm discontinued due to AE prior to the initiation of treatment. Among all randomized population, 100% and 98.2% were treated in treatment and control arm, respectively and 75.5% and 45.5% of the randomized patients were still ongoing by the second interim clinical cutoff date. The following table also summarizes patient who met the primary endpoint and discontinued the study:

Table 4: Applicant's summary of Disposition of Subjects (ITT Analysis Set)

Subject Disposition, n (%)		IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
Randomized		110 (100%)	110 (100%)	220 (100%)
Randomized but Not Treated		0	2 (1.8%)	2 (0.9%)
Treated		110(100%)	108(98.2%)	218(99.1%)
Ongoing on Study		83(75.5%)	50(45.5%)	133(60.5%)
Met Primary Study Endpoint and discontinued study	Total	12(10.9%)	50(45.5%)	62(28.2%)
	Disease Progression	7(6.4%)	41(37.3%)	48(21.8%)
	Death	5(4.5%)	9 (8.2%)	14 (6.4%)

Discontinued Study	Total	15 (13.6%)	10 (9.1%)	25 (11.4%)
	Adverse Events	5 (4.5%)	6 (5.5%)	11 (5.0%)
	Physician Decision	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Withdrawal by Subject	9 (8.2%)	3 (2.7%)	12 (5.5%)

In general, the distribution of baseline disease characteristics based on intent-to-treat population also appears to be balanced between treatment arms. Table 5 below summarizes the baseline disease characteristics. The median time since diagnosis was 94.2 vs. 103.1 months (~7.9 vs. 8.6 years) for treatment and control arms, respectively indicating that the patients presented with CLL for an extensive period prior to study entry. The majority of patients had advanced disease with 64.6% Rai Stage III or IV and 55.9% Binet Stage C.

Table 5: Applicant's summary of CLL Disease History (ITT Analysis Set)

		IDELA + R (N=110)	**Placebo + R (N=110)**	**Total (N=220)**
Time since diagnosis	N	110	110	220
	Mean(Std Dev)	108.3 (62.28)	106.4 (52.73)	107.4 (57.58)
	Median	94.2	103.1	102.0
	Q1, Q3	69.4, 142.2	64.2, 144.3	65.8, 143.9
	Min, Max	7.6, 318.7	8.6, 248.8	7.6, 318.7
Rai Stage at Screening	0	0	1 (0.9%)	1 (0.5%)
	I	18 (16.4%)	19 (17.3%)	37 (16.8%)
	II	16 (14.5%)	10 (9.1%)	26 (11.8%)
	III	22 (20.0%)	18 (16.4%)	40 (18.2%)
	IV	48 (43.6%)	54 (49.1%)	102 (46.4%)
	Not Available	0	0	0
	Missing	6 (5.5%)	8 (7.3%)	14 (6.4%)
Binet Stage at Screening	A	7 (6.4%)	4 (3.6%)	11 (5.0%)
	B	29 (26.4%)	32 (29.1%)	61 (27.7%)
	C	63 (57.3%)	60 (54.5%)	123 (55.9%)
	Not Available	0	0	0
	Missing	11 (10.0%)	14 (12.7%)	25 (11.4%)

The demographic and baseline characteristics of the subjects are summarized in Table 6. In general, the distribution of the demographic characteristics, including gender, race, age and KPS appears to be comparable between treatment arms (shown in the following table). The majority of patients were White (90%). There were more patients 65 years or older than patients aged less

than 65 years (78% vs. 22%) and more men than women (65% vs. 35%) in this study. Approximately, 75.9 %(72.7% vs. 79.1%) patients had KPS score of 80% or higher and appears to be distributed among the higher scores approximately in the same ratio between both the treatment arms.

Table 6: Key baseline and demographic and disease characteristics

Variable		IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
Gender	Males	76 (69.09%)	68 (61.82%)	144 (65.45%)
	Female	34 (30.91%)	42 (38.18%)	76 (34.55%)
Race	White	100 (90.91%)	98 (89.09%)	198 (90.00%)
	Black or African American	3 (2.73%)	3 (2.73%)	6 (2.73%)
	Other	2 (1.82%)	2 (1.82%)	4 (1.82%)
	Not Permitted	5 (4.55%)	7 (6.36%)	12 (5.45%)
Age Group	< 65 yrs	22 (20.00%)	27 (24.55%)	49 (22.27%)
	>=65 yrs	88 (80.00%)	83 (75.45%)	171 (77.73%)
	>= 70 yrs	63 (57.27%)	59 (53.64%)	122 (55.45%)
	< 70 yrs	47 (42.73%)	51 (46.36%)	98 (44.55%)
Age	N	110	110	220
	Mean	71	70	70
	Std Dev	7.7	8.11	7.9
	95% CI for Mean	70, 72	69, 72	69,72
	Median	71	71	71
	Min, Max	48, 90	47, 92	47,92
BMI	N	110	110	220
	Mean	26.81	25.85	26.33
	Std Dev	5.64	4.77	5.23
	95% CI for Mean	25.74, 27.82	24.95, 26.75	25.63, 27.02
	Median	25.45	25	25.3
	Min, Max	19.4, 49.5	11.7, 42.2	11.7, 49.5
Karnofsky Performance	40	1 (0.91%)	1 (0.91%)	2 (0.91%)
	50	3 (2.73%)	4 (3.64%)	7 (3.18%)
	60	6 (5.45%)	5 (4.55%)	11 (5.00%)
	70	20 (18.18%)	13 (11.82%)	33 (15.00%)
	80	42 (38.18%)	46 (41.82%)	88 (40.00%)

	90	23 (20.91%)	28 (25.45%)	51 (23.18%)
	100	15 (13.64%)	13 (11.82%)	28 (12.73%)

Approximately 43.2% subjects had 17p deletion and/or *TP53* mutation (41.8% vs. 44.6%) and most subject had unmutated *IGHV* status (83.6% overall). Nearly all subjects had received prior anti-CD20 therapy (95.9%).

Table 7: Summary of stratification factors using the CRF data

Stratification variable	Stratification Value	IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
17p Deletion/p53 Mutation	Either	46 (41.82%)	49 (44.55%)	95 (43.18%)
	Neither	64 (58.18%)	61 (55.45%)	125 (56.82%)
IgHV Region Mutation	Mutated	19 (17.27%)	17 (15.45%)	36 (16.36%)
	Unmutated	91 (82.73%)	93 (84.55%)	184 (83.64%)
Prior anti-CD20 therapy?)	Yes	107 (97.27%)	104 (94.55%)	211 (95.91%)
	No	3 (2.73%)	6 (5.45%)	9 (4.09%)

Reviewer's comment: Prior anti-CD20 therapy status was not used as stratification factor in the stratified analysis because only < 5% of the patients did not take anti-CD20 therapy.

3.2.3 Statistical Methodologies

To perform the analysis of primary and secondary endpoints, the analysis sets defined in section-3.2.1 are used. The ITT analysis set was used in the analyses of subject characteristics, PFS, ORR, OS, and CR rate. The PP analysis set was used in sensitivity analyses of the primary and secondary efficacy endpoints: PFS, ORR, and LNR. The safety analysis set was used in the analyses of safety variables as well as study treatment administration, post-study therapy, and health economic variables.

Analysis methods for primary efficacy endpoint(PFS):

PFS between the 2 treatment arms was compared, based on the ITT analysis set using a stratified log-rank test, adjusted for the stratification factors (17p deletion and/or *TP53* mutation status and *IGHV* mutation status) used for randomization. Medians, the proportion of subjects with events and those who were censored, hazard ratios and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) were presented. The Kaplan-Meier curve was also plotted.

Censoring:

Data will be censored on the date of the last tumor assessment (including assessments with a not evaluable [NE] outcome) for subjects

- who do not have disease progression or die after study discontinuation, or
- who start new anti-tumor therapy prior to documented disease progression, or
- who have ≥2 consecutive missing tumor assessments before disease progression or death.

Subjects without adequate baseline tumor response evaluation will be censored on the randomization date.

Sensitivity Analysis for primary endpoint:

To assess the robustness of the primary PFS results, the following exploratory sensitivity analyses will be performed:

- PFS will be compared between the treatment arms in the ITT analysis set using the unstratified log-rank test.

- PFS will also be compared between treatment arms in the PP analysis set using Kaplan-Meier method and the stratified log-rank test.

- PFS will be further analyzed by censoring data from surviving, non-progressing subjects only at the last time that lack of definitive CLL progression was objectively documented. An additional worst-case sensitivity analysis will be performed in which surviving, non-progressing subjects who are lost to follow-up are categorized as having an event at the time of the last known CLL tumor status assessment if they were in the treatment arm and are categorized as censored at the time of the last known CLL tumor status assessment if they were in the control arm. These analyses will be performed based on the ITT analysis set using Kaplan-Meier method and the stratified log-rank test.

Reviewer's comments: Additional sensitivity analysis was conducted to evaluate the robustness of the efficacy results as stated below:

- *A sensitivity analysis was performed to assess the robustness of the PFS results based on investigator evaluated PFS using the ITT analysis set and stratified log-rank test.*

- *An exploratory analysis was also performed based on the Cox's proportional hazards model including some additional baseline subject characteristics (i.e., gender, age, race, number of prior therapies, disease staging, etc.) as covariates to identify potential prognostic factors beyond the stratification factors. A stepwise selection*

procedure was used with significance level for entry of 0.20 and a significance level for stay of 0.10.

- *Additional sensitivity analysis on PFS and ORR was performed by dropping the Site-6708 due to potential concerns about the study conduct.*

- *Applicant performed the primary and secondary analyses using the actual strata values recorded in the CRF. To verify the appropriateness of using CRF recorded strata values, an analysis was performed to assess the difference between the two sources of stratification, CRF vs. IVRS. If there was no significant difference then the analyses will be conducted using the applicant proposed stratification factor i.e. CRF recorded strata values otherwise a sensitivity analyses will be performed using the IVRS recorded stratification to assess for the difference in the primary efficacy results.*

Analysis methods for secondary efficacy endpoints:

ORR: Differences in number and percentage of subjects between the treatment arms in ORR were compared using CMH Chi-square tests after adjusting for stratification factors. Odds ratios and the corresponding 95% CIs were also presented. The ORR analysis used the IRC assessments based on the ITT analysis set. Sensitivity analyses were performed using the IRC assessments based on the PP analysis set and were performed based on the investigators assessments using the ITT analysis set.

LNR: Differences in LNR between the 2 treatment arms were compared using CMH Chi-square tests after adjusting for stratification factors. Only subjects that had both baseline and ≥1 evaluable post-baseline greatest perpendicular diameters (SPD) were included in this analysis.

OS: The OS analysis (i.e., under alpha-protection) was performed using the ITT analysis set(according to the original randomization) which included all available survival information from Study GS-US-312-0116 with long-term follow-up, and its companion Study GS-US-312-0117 with long-term follow-up, up to the data cut-off date of 09 October 2013. Data from surviving subjects was censored at the last time that the subject was known to be alive on study (including all the in-person visit dates captured in the datasets, i.e., BM biopsy, central lab collection, CT scan, physical exam, drug administration in clinic, concomitant medication and therapy start date, ECG, PRO collection, long term follow up, hospitalization, transfusion, pregnancy testing). Differences between treatment arms in OS were assessed in the ITT analysis set using a stratified log-rank test, adjusted for stratification factors of 17p deletion and/or TP53 mutation status and IGHV mutation status. Plots of time to event by treatment arm were produced using the Kaplan-Meier method. Proportion of subjects who were censored, proportion

of OS events, medians, hazard ratios and corresponding 95% CIs were presented by treatment arm. In addition, a sensitivity OS analysis was performed using the same approach as the first OS analysis by including survival information from Study GS-US-312-0116 with long-term follow-up to the data cut-off date of 09 October 2013.

CR: CR analysis was not performed because there were no CR events observed as of the cut-off date of 09 October 2013.

Reviewer's comments:

- *The primary and secondary endpoint analysis are performed using the IVRS recorded stratification factors since there is a small difference in the number of subjects categorized using the IVRS recorded stratification factors compared to CRF. The differences are illustrated in the results Section-3.2.4.*

- *FDA does not agree with the inclusion of the Study GS-US-312-117 data for the analysis of OS due to the concern of confounding effect (i.e. control arm crossing over to take Idela) from the combined analysis. So the FDA's OS analysis will be based on Study GS-US-312-116 data alone.*

- *It is noted that the study was not powered based on the overall survival analysis.*

Subgroup Analyses:

All subgroup efficacy analyses were performed using IRC assessments of PFS if there was sufficient sample size in the subgroup. Primary and secondary efficacy endpoints were examined in the following subgroups:

- Stratification factors:
    - 17p deletion and/or *TP53* mutation in CLL cells: either versus neither (or indeterminate)
    - *IGHV* mutation: unmutated (or *IGHV*3-21) versus mutated (or indeterminate)
- 17p deletion (Yes or No [including indeterminate])
- Gender (Male or Female)
- Age group (< 65 or ≥ 65)
- Race (White or Non-White)

3.2.4 Results and Conclusions

The final efficacy analysis was originally planned to be conducted after approximately the 119th PFS event had occurred, unless a decision had been made to stop the trial based on an interim analysis. Two formal interim efficacy analyses were planned after approximately the 60th (50%) and 90th (75%) PFS event had occurred. Based on the first interim analysis, with a data cutoff date on 30 August 2013, results of the primary endpoint (PFS), p-value < 0.0001, p-value crossed the pre-specified alpha boundary of 0.001 and hence a decision was made to stop the blinded-phase of the study after the first interim analysis. A second analysis of the blinded-phase was performed based on a data cut-off date of 9 October 2013. Between the first and second interim analyses, the double-blind was maintained for all subjects, investigators, the CRO, and all personnel involved in the conduct of the trial. Only one statistician and one medical writer of the applicant's personnel were unblinded after the DMC recommendation to stop the trial at the first interim analysis.

In this section, the first interim results were summarized briefly and the second interim results were presented in a tabular format for the primary and secondary endpoints.

Median (95% CI) follow-up time in months for Idela arm was 5.5(4.4, 6.3) months and 4.6(3.9, 5.6) months for the control arm.

Primary endpoint analysis results:

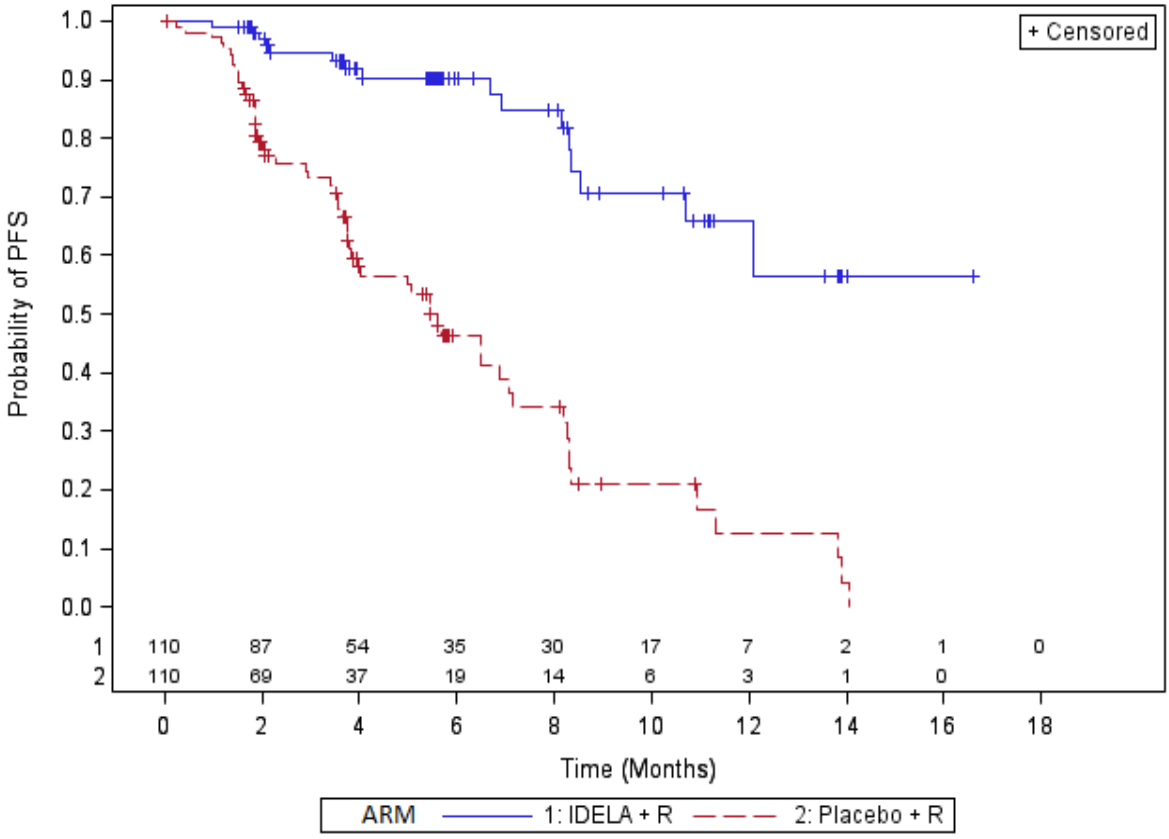
PFS: Based on the first interim analysis result, the study demonstrated a statistical significant effect in favor of the Idela treated arm (p<0.0001). The hazard ratio estimate was 0.15[95% CI=(0.08, 0.28)] and the estimated median PFS was not reached for the Idela treatment arm, however, for the control arm the medina PFS time was 5.5 months. Table 8 below summarizes the second interim results for PFS.

Table 8: PFS Efficacy Results for the second interim data

		IDELA + R (N=110)	Placebo + R (N=110)
Number of Subjects with Events	Total	16(14.54%)	59(53.63%)
	Disease Progression	11(10%)	51(46.36%)
	Death	5(4.55%)	8(7.27%)
Number of Subjects Censored	Total	94(85.45%)	51(46.36%)
	Ongoing	82(74.55%)	46(41.82%)
	Discontinued Study	12(10.91%)	5(4.55%)

KM Estimates	Median(95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
Adjusted Hazard Ratio(95% CI)		0.18(0.10,0.32)	
P-val (Stratified log-rank test)		<0.0001	

Figure 1: Kaplan-Meier Curve of Progression Free Survival for the second interim results



The second interim results demonstrated a statistical significant progression free survival result with hazard ratio 0.18[95% CI= (0.10, 0.32); p<0.0001 based on stratified log-rank test] in favor of Idela treated arm and the Kaplan-Meier plot is given in Figure 1.

Reviewer's comment:
Based on the SAP, patients were censored if they received another antitumor treatment and/or missed ≥2 consecutive tumor measurements. However, there were no patients who met the above two criteria and hence these two censored categories were missing in the above table. It was noted that there was only 1 patient who were identified as ever taken any anti-cancer therapy based on the ADCM (ADAM dataset) data. It is possible that the data capture may not be

completed for the concomitant medication data (as presented in ADCM) at the time of the second interim analysis.

Sensitivity Analysis for PFS:

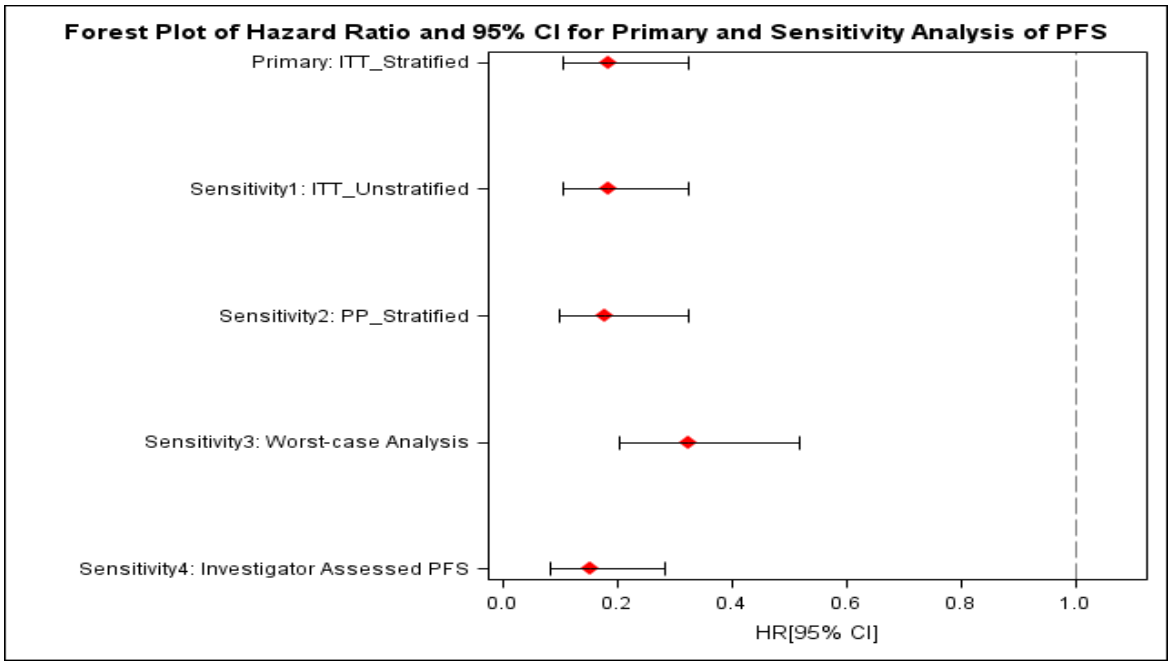
Sensitivity analyses for PFS were performed as defined in section 3.2.3 and the results were summarized in the following table.

Table 9: Sensitivity Analysis of PFS for the second interim data

Sensitivity Analysis	#events/total	Hazard Ratio(95% CI)	Median (95% CI)	
			Idela + R	Placebo + R
Primary	16/110 : 59/110	0.179 (0.1 ,0.319)	NR (10.71, NR)	5.45 (3.78, 7.06)
ITT_Unstratified	16/110 : 59/110	0.186 (0.107 ,0.324)	NR (10.71, NR)	5.45 (3.78, 7.06)
PP_Stratified	16/110 : 56/110	0.181 (0.101 ,0.324)	NR (10.71, NR)	5.58 (3.81, 7.06)
Worst-case Analysis	28/110 : 59/110	0.325 (0.204 ,0.518)	11.20(8.35, NR)	5.45(3.78, 7.06)
Investigator Assessed PFS	16/110 : 58/110	0.154 (0.084 ,0.284)	NR(11.07, NR)	5.49(3.75, 7.29)

The forest plot of hazard ratio and the corresponding 95% confidence intervals were plotted in Figure- for the primary and each of the sensitivity analyses.

Figure 2: Sensitivity analysis of PFS for the second interim results



Reviewer's comments:
The results based on the applicant's pre-specified sensitivity analyses are supportive to the primary efficacy results of PFS favoring the Idela treatment arm.

- *The sensitivity analysis performed on the investigator evaluated PFS to assess the robustness of the PFS resulted in an estimated hazard ratio of 0.154 [95% CI= (0.084, 0.284)] which further supports the primary efficacy results.*

- *The exploratory analysis performed to identify the potential prognostic factors among stratification factors, Rai and Binet staging at screening, number of prior therapies, age, and gender using the Cox's proportional hazards model selected the stratification factor '17p Deletion/p53 Mutation' as significant. After adjusting, the treatment remained significant with p-value < 0.0001 and the adjusted hazard ratio estimate for treatment was 0.206[95% CI= (0.115, 0.367)]. However, it is noted that the results were not based on the ITT population since there was approximately 13% of the missing covariate data.*

- *The additional sensitivity analysis on PFS and ORR performed by dropping the site 6708 (per request from the medical reviewer; for potential study conduct concern) were in concurrence with the primary efficacy results [HR=0.16, 95% CI for HR=(0.09,0.29); p-value < 0.0001]*

- *The primary and secondary analyses are performed by using the actual strata values recorded in the CRF. The recorded values for the IgHV mutation stratification factors are exactly same on the CRF and IVRS sources of stratification, however, there exists a small difference in the values for the 17p Deletion/p53 Mutation in CLL cells when compared to the IVRS recorded stratification data. The below table summarizes these stratification factors.*

Table 10: CRF vs. IVRS stratification

Stratification factor	***Stratification factor Values***	***Stratification Source***	
		CRF	***IVRF***
IgHV mutation	*Mutated*	*36*	*36*
	Unmutated	*184*	*184*
17p Deletion/p53 Mutation	*Either*	*95*	*91*
	Neither	*125*	*129*

It was noted that there was not much difference in the stratification factor data from CRF and IVRS; hence sensitivity analysis stratified by the stratification factors from IVRS data will not be performed.

Secondary endpoints analyses results:

In this section, the analysis results for the key secondary endpoints ORR, LNR and OS were presented. There were no CR events observed based on the secondary interim data and hence CR analysis was not presented. For analysis purpose, the results for duration of response (DOR) were summarized by median DOR, 95% CI and p-value of the unstratified log-rank test.

Table 11: Best Overall Response Rates for the second interim analysis

Analysis Variable		**IDELA + R (N=110)**	**Placebo + R (N=110)**
Best Overall Response	Partial Response (PR)	82(74.55%)	16(14.55%)
	Stable Disease (SD)	19(17.27%)	68(61.82%)
	Progressive Disease (PD)	1(0.91%)	17(15.45%)
	Not Evaluable (NE)	8(7.27%)	9(8.18%)

Based on the first interim results, the rate of overall response rate was 64.5% in the Idela treatment arm and 10% in the control arm with an estimated odds ratio of 16.8[95% CI= (7.89, 35.81)] from the ITT population. The p-value from the CMH test for ORR is <0.0001 favoring the results of Idela treatment arm compared to the control arm. Similarly, for the lymph node responses, proportion of responses was 71.8% and 2.7% for Idela and control arms respectively. The p-value from the CMH test for LNR is <0.0001 indicating a statistical significance results for Idela treatment arm compared to the control arm. The results based on the second interim results are presented in the following table. These results were consistent with the findings from the first interim analysis.

Table 12: ORR, LNR and DOR analysis results for second interim results

Analysis Variable		**IDELA + R (N=110)**	**Placebo + R (N=110)**
ORR	**#events/N**	82/110(74.5%)	16/110(14.5%)
	%Responses(95% exact CI)	74.5%(65.4,82.4)	14.5% (8.5,22.5)
	p-val(CMH test)	< 0.0001	
LNR	**#events/N**	94/110(85.5%)	6/110(5.5%)
	%Responses(95% exact CI)	85.5%(77.5, 91.5)	5.5%(2.0,11.5)
	p-val(CMH test)	< 0.0001	
DOR	**Median (95% CI)**	NR(10.45, NR)	5.6(2.79, 6.37)

Reviewer's comments:

- *The results based on the applicant's pre-specified sensitivity analyses based on PP population are supportive to the primary efficacy results of ORR and LNR favoring the Idela treatment arm.*

- *As per the comments from medical review, LNR analysis was not consistent with the assessment of the standard response criteria. Lymph node response is not acceptable because it focuses on only one aspect of multi-systemic disease involvement.*

The p-value from the stratified log-rank test for OS based on first interim data was 0.018 with an estimated hazard ratio of 0.28[95% CI= (0.09, 0.86)]. The second interim results for the OS are summarized in the below table.

Table 13: OS Efficacy Results for the second interim analysis based on Study GS-US-312-0116 and Study GS-US-312-0117

		IDELA + R (N=110)	**Placebo + R (N=110)**
Number of Subjects with Events	Total	6(5.5%)	20(18.2%)
Number of Subjects Censored	Total	104 (94.5%)	90 (81.8%)
	Ongoing	83 (75.5%)	50 (45.5%)
	Discontinued Study	21 (19.1%)	40 (36.4%)
K-M estimate	Median(95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
Adjusted Hazard Ratio(95% CI)		0.28 (0.11, 0.69)	
P-val (Stratified log-rank test)		0.003	
P-val (Unstratified log-rank test)		0.003	

Reviewer's Comment:
Applicant's analysis results for overall survival are based on the combined data from study GS-US-312-0116 and the extension study GS-US-312-0117. Thus, there is a chance of confounding effect since patients treated with placebo were allowed to cross over to receive Idela therapy. OS analysis was requested based on only Study GS-US-312-0116 which was specified as sensitivity analysis for OS by the applicant. The results of the Study GS-US-312-0116 are presented below:

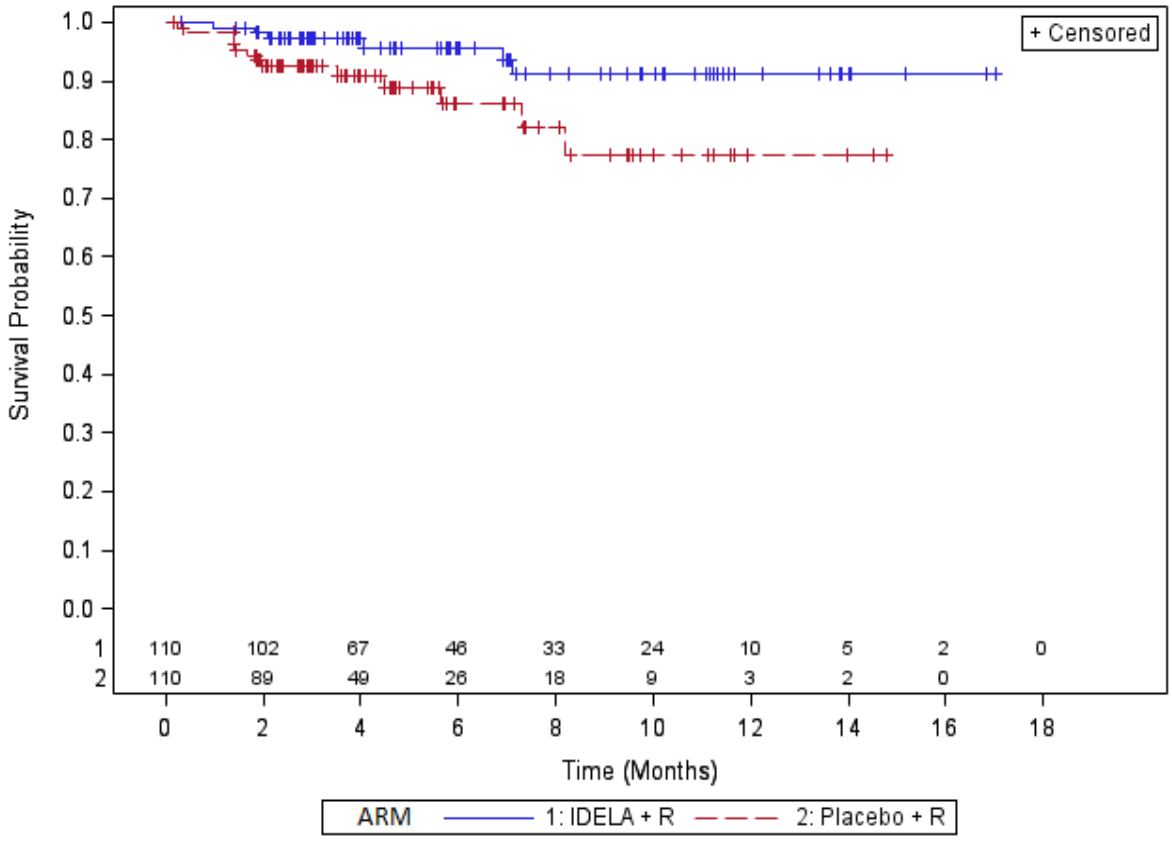
Table 14: OS Efficacy Results for the second interim analysis based on study GS-US-312-0116

		IDELA + R (N=110)	***Placebo + R (N=110)***
Number of Subjects with Events	*Total*	*6(5.5%)*	*13(11.8%)*

Number of Subjects Censored	*Total*	*104 (94.5%)*	*97 (88.2%)*
	Ongoing	*83 (75.5%)*	*50 (45.5%)*
	Discontinued Study	*21 (19.1%)*	*47 (42.7%)*
K-M estimate	*Median (95% CI)*	*NR*	*NR*
Adjusted Hazard Ratio(95% CI)		*0.37(0.14, 0.98)*	
P-val (Stratified log-rank test)		*0.0370*	
P-val (Unstratified log-rank test)		*0.0351*	

The median overall survival was not reached in both the arms. The p-value from the stratified log-rank test based on the Study GS-US-312-0116 alone is 0.037 and that of unstratified test is 0.0351. Based on these p-values and the discussion below, the significance of OS in the Idela treatment arm appears to be nominal (b) (4) *Additional labelling recommendations are summarized in Section-5.4.*

Figure 3: Kaplan-Meier Curve of Overall Survival



The applicant submitted a simulation study on 06 April 2014 to justify that the Type I error is adequately controlled for the OS analysis at a significance level of 0.034(Refer to Figure 5). However, they demonstrated through simulation results that the type-I error rate is not adequately controlled at the pre-specified significance level of 0.05 as shown in Figure 4.

The agency made additional information requests to the applicant on 1May 2014 by providing analytical expressions to derive the type I error. In response, the applicant provided the analytical type-I error results using both the 0.05 significance level and the modified post-hoc significance level of 0.034. The analytical results agreed with the simulations provided earlier and the type-I error rate exhibited the same pattern as shown in Figure 4 and Figure 5.

The applicant claims that Type I error may be controlled if the significance level of 0.034 had been used. This statistical reviewer concludes that an adjusted P-value cannot be calculated due to lack of a pre-specified alpha spending plan for OS. Also, in clinical perspective, the agency considers that the results may not be reliable or reproducible due to the small number of deaths.

Figure 4: Type I Error Rate of OS with the Pre-Specified Testing Strategy of 0.05 significance level

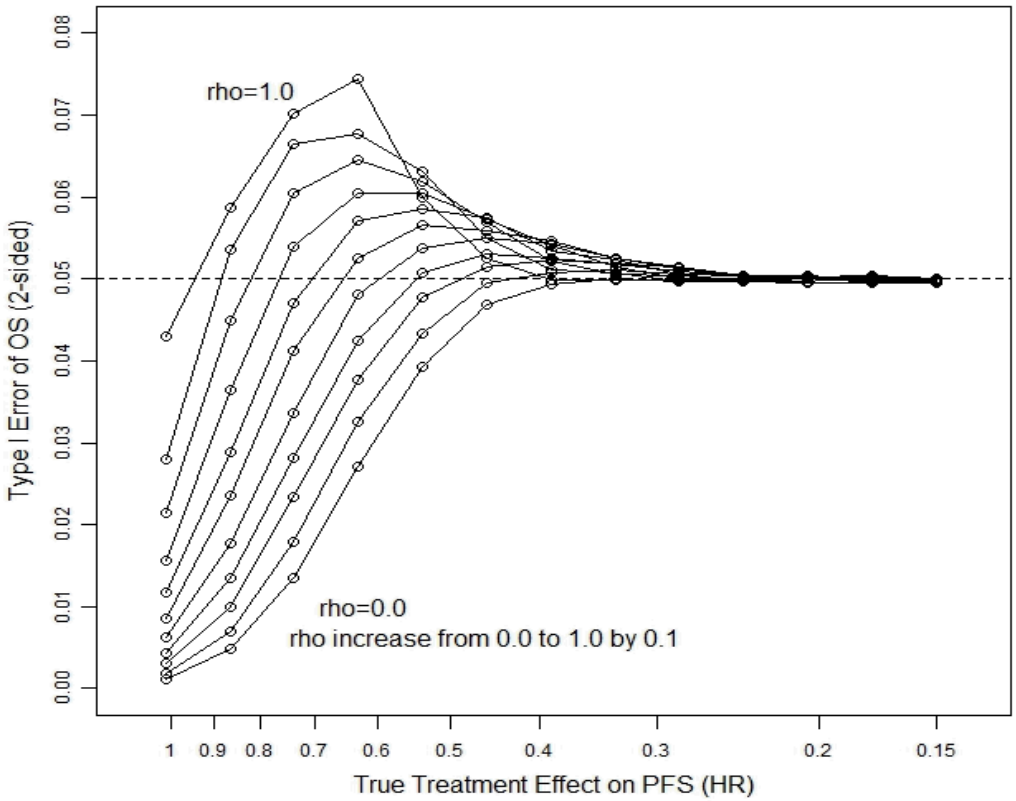
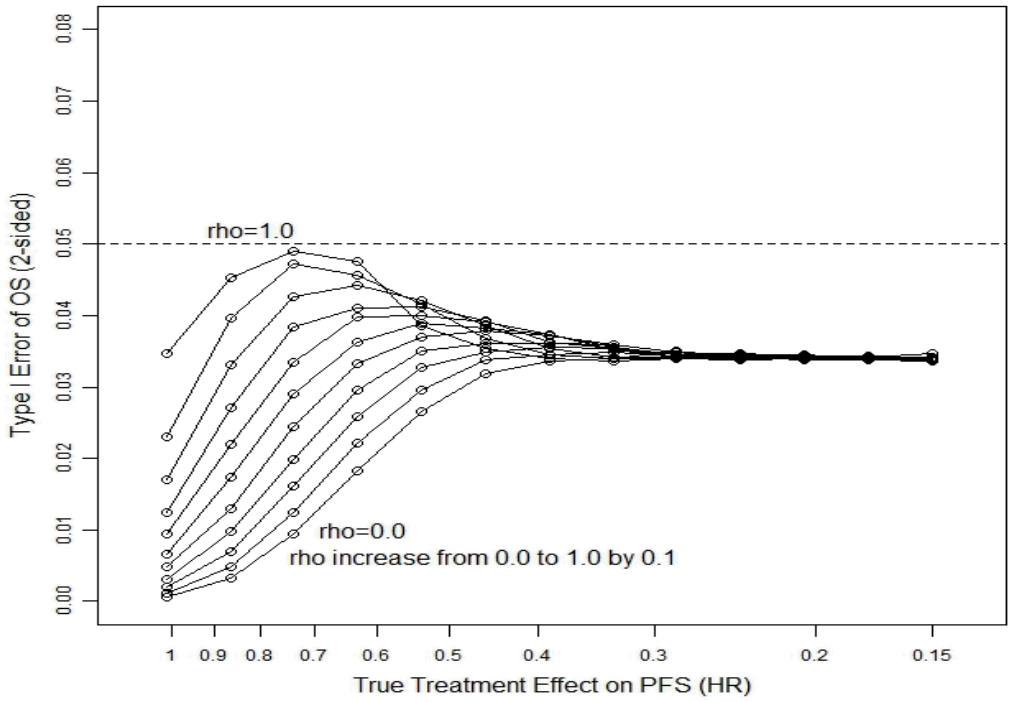


Figure 5: Type I error rate of OS with the modified testing strategy of 0.034 significance level



3.3 Evaluation of Safety

The safety assessment is deferred to the clinical judgment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis results based on the following factors were examined for the primary and secondary efficacy endpoints:

- Stratification factors:
  - 17p deletion and/or *TP53* mutation in CLL cells: either versus neither (or indeterminate)
  - *IGHV* mutation: unmutated (or *IGHV*3-21) versus mutated (or indeterminate)
- 17p deletion (Yes or No [including indeterminate])
- Gender (Male or Female)
- Age group (< 65 or ≥ 65)
- Race (White or Non-White)

All subgroup efficacy analyses were performed using IRC assessments if there was sufficient sample size in the subgroup. The hazard ratio estimates based on PFS and the corresponding 95% confidence intervals for each subgroup were summarized in Table 15.

Table 15: Subgroup analysis results of PFS for the second interim analysis

Subgroup	level	Count	Sample size	Hazard Ratio	95% CI		HR(LL, UL)
					LL	UL	
Age group	<65	48	5/21:14/27	0.306	0.108	0.871	0.31(0.11,0.87)
	≥65	172	11/89:45/83	0.145	0.072	0.292	0.15(0.07,0.29)
17p deletion	No	163	13/84:37/79	0.228	0.121	0.432	0.23(0.12,0.43)
	Yes	57	3/26:22/31	0.108	0.032	0.368	0.11(0.03,0.37)
17p Deletion/p53 Mutation	Either	95	7/46:34/49	0.163	0.072	0.372	0.16(0.07,0.37)
	Neither	125	9/64:25/61	0.219	0.101	0.475	0.22(0.10,0.47)
IgHV mutation	Mutated	36	5/19:8/17	0.645	0.196	2.122	0.64(0.20,2.12)
	Unmutated	184	11/91:51/93	0.136	0.07	0.265	0.14(0.07,0.26)
Race	White	198	16/100:51/98	0.224	0.127	0.395	0.22(0.13,0.39)
	Non-White	22	0/10:8/12	0	-	-	-
Region	US	163	14/80:46/83	0.207	0.113	0.379	0.21(0.11,0.38)
	Non-US	57	2/30:13/27	0.09	0.02	0.401	0.09(0.02,0.40)
Gender	Female	76	7/34:20/42	0.308	0.128	0.739	0.31(0.13,0.74)
	Male	144	9/76:39/68	0.139	0.067	0.29	0.14(0.07,0.29)

Reviewer's comment:

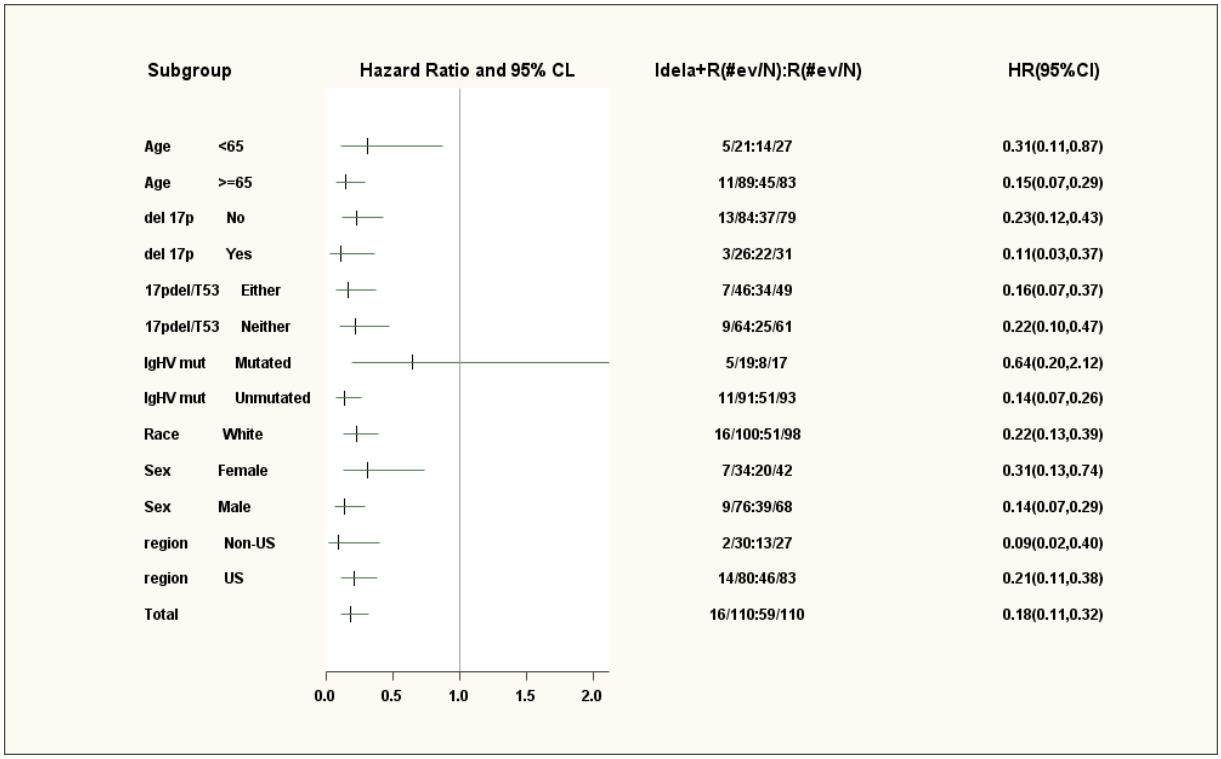
- *The upper bound of the 95% CI of hazard ratio estimates was less than one for all the subgroups, except for IgHV mutated group, favoring the Idela treatment arm compared to the control arm.*

- *However, the interpretation of the IgHV mutated subgroup should be performed with caution since it has only 16% of the randomized patients resulting in a wider confidence interval.*

- *Furthermore, the non-whites subgroup of race has only 10% of the patients with no patients being randomized to the Idela treatment.*

Forest plots of the hazard ratio estimates based on PFS and the corresponding 95% confidence intervals for each subgroup summarized in Table 15 are presented below:

Figure 6: Forest Plot for the subgroup analysis of PFS



4.1 Gender, Race, Age, and Geographic Region

Gender

The hazards ratio estimates of PFS for male and female subgroups were equal to 0.14[95% CI=(0.07, 0.29)] and 0.31[95% CI=(0.13, 0.74)] .The upper bound of the 95% CIs being less than 1 favors treatment effect in the Idela treatment arm for both gender subgroups.

Table 16: Reviewer's Summary of Hazard Ratios for PFS by Gender

		IDELA + R (N=110)	Placebo + R (N=110)
Male	# events /total	9/76	39/68
	Adjusted HR(95% CI)	0.14(0.07, 0.29)	
Female	# events /total	7/34	20/42
	Adjusted HR(95% CI)	0.72(0.56,0.93)	

Race

The hazard ratio estimates of PFS for the White subgroup was smaller than 1 which demonstrates favorable treatment effect in the Idela treatment arm. There were no events observed in the Idela treatment arm for Non-White subgroup and hence the hazard ratio was not calculated.

Table 17: Reviewer's Summary of Hazard Ratios of PFS by Race

		IDELA + R (N=110)	**Placebo + R (N=110)**
Whites	# events /total	16/100	51/98
	Adjusted HR(95% CI)	0.22(0.13, 0.39)	
Non-Whites	# events /total	0/10	8/12
	Adjusted HR(95% CI)	-	

Age groups

The hazard ratio estimates based on PFS for both age subgroups (<65 years and ≥65 years old) were less than 1 which showed a more favorable result observed in the Idela treatment arm compared to the control arm. Patients who were 65 years or older appear to have a smaller hazard ratio estimate.

Table 18: Reviewer's Summary of Hazard Ratios of PFS by Age group

		IDELA + R (N=110)	Placebo + R (N=110)
<65 years	# events /total	5/21	14/27
	Adjusted HR(95% CI)	0.31(0.11,0.87)	
≥65 years	# events /total	11/89	45/83
	Adjusted HR(95% CI)	0.15(0.07,0.29)	

Geographic Region:

The hazard ratio estimates based on PFS for both the regions of US and Non-US were 0.21(0.11, 0.38) and 0.09(0.02, 0.40) respectively. The results were in favor of the Idela treatment arm compared to the control arm. US patients appear to have a larger hazard ratio estimate of 0.21 compared to the 0.09 for Non-US patients.

Table 19: Reviewer's Summary of Hazard Ratios of PFS by Region

		IDELA + R (N=110)	Placebo + R (N=110)
US	# events /total	14/80	46/83
	Adjusted HR(95% CI)	0.21(0.11,0.38)	
Non-US	# events /total	2/30	13/27
	Adjusted HR(95% CI)	0.09(0.02,0.40)	

Reviewer's comment:
However, because of the nature of the subgroup analyses and a smaller sample size in some of the subgroups analyzed above, the interpretation of the differential treatment effect among subgroups should be considered with caution.

5 SUMMARY AND CONCLUSIONS

5.1 Summary

Based on study GS-US-312-0116, the results showed significant improvement of the progression free survival. Based on the first interim analysis result, the study demonstrated a statistical significant effect in favor of the Idela treated arm (p-value <0.0001) with the hazard ratio estimate of 0.15[95% CI= (0.08, 0.28)].

For the second interim results, the hazard ratio estimate for PFS was 0.18[95% CI= (0.10, 0.32); p-value <0.0001] in favor of the treatment arm and the median PFS time was not reached [95% CI= (10.7, NR)] in the treatment arm whereas it is 5.5 months [95% CI=(3.8, 7.1)] in the control arm. The favorable results from the treatment arm were robust based on various sensitivity analyses and consistent results were shown throughout various subgroups. The result based on the objective response rate (ORR=74.5% vs. 14.5% for treatment and control arm, respectively; p-value <0.0001) and the lymph node response (LNR=85.5% vs. 5.5% for treatment and control arm, respectively; p-value <0.0001) also demonstrates statistical significance in favor of the treatment arm. The results based on overall survival were HR=*0.37*, 95% CI= *(0.14, 0.98)*; p-value 0.037. A summary of these primary efficacy results is shown in Table 20.

Table 20: Reviewer's Summary of PFS, ORR, LNR and OS based on second interim results

Endpoint		Idela + R N=110	Placebo + R N=110
PFS	Number (%) of events Progressive disease or death	16(77)	59 (83)
	Duration of progression free survival (mon.) Median (95% CI) [a]	NR (10.7, NR)	5.5 (3.8, 7.1)
	Adjusted Hazard ratio (95% CI)[c]	0.18 (0.10, 0.32)	
	p-value [b]	<0.0001	
ORR	Objective response rate 95% CI	82 (74.5%) (65.4%, 82.4%)	16 (14.5 %) (8.5%, 22.5 %)
	p-value (Chi-square test)	<0.0001	
LNR	Objective response rate 95% exact CI	94 (85.5%) (77.5%, 91.5%)	6 (5.5%) (2.0%, 11.5%)
	p-value (Chi-square test)	<0.0001	
OS	Number (%) of events[d] Deaths	6 (5.5%)	13 (11.8%)
	Adjusted Hazard ratio (95% CI)[c]	0.37(0.14, 0.98)	

CI=confidence interval;
a Median and percentiles are based on Kaplan-Meier survival estimates.
b Stratified log rank test, stratified by 17p deletion and/or p TP53 mutation in CLL cells (either vs neither) and IGHV mutation(unmutated vs mutated).
c Estimated using the Cox proportional hazard model stratified by the stratification factors.
d results based on study GS-US-312-0116 alone.

However, significance of LNR and OS results were inconclusive based on first or the second interim analyses since LNR analysis was not consistent with the assessment of the standard response criteria and whether or not OS result is significant at the first or the second interim analyses cannot be determined since the significance level for interim analysis of OS was not pre-specified.

While the OS results may appear not to inflate the type I error if a significance level as small as 0.034 was used (post hoc, applicant's position as discussed in Section 3.2.4), due to the small number of events, significance levels for the interim analysis was not pre-specified and the concern that the actual effect may be over-estimated at the interim analysis and may not be reproducible, (b) (4)

Based on hazard ratio estimates from subgroup analyses, Idela treatment arm appears to have longer progression free survival across various demographic and stratification factors subgroups.

5.2 Statistical Issues and Collective Evidence

The main issue from this study is the concern of the patients included with no post-baseline assessments challenging the completeness of data during the interim analysis. For the first

interim analysis there were 20% (44/220 patients) who were newly enrolled before the data cutoff date of 30 August 2013 and hence did not have post-baseline assessments. In addition, OS results for the second interim were preformed based on the combined data from the pivotal study GS-US-312-0116 and the extended phase study GS-US-312-0117. Only the OS results based on the study GS-US-312-0116 was considered for the analysis in order to avoid the potential confounding effect due to the crossover of the placebo arm to the Idela treatment arm. . (b) (4)

5.3 Conclusions and Recommendations

In summary, based on study GS-US-312-0116, the results demonstrated statistically significant improvement on progression free survival, objective response rate and lymph node response for the Idela treatment arm. The results appear to be robust based on sensitivity analyses including the analyses using different database cutoff dates. The results also appear to be consistent across various subgroups. However, whether or not the overall survival result is significant based on the first or second interim analysis is not clear because the significance level for interim analysis of OS was not pre-specified.

In conclusion, this statistical reviewer confirms the applicant's results submitted. Whether the results demonstrate an overall favorable benefit to risk ratio in supporting an indication of the Idela + rituximab treatment in patients with previously treated chronic lymphocytic leukemia will defer to the clinical review team.

5.4 Labeling Recommendations

This statistical review supported the inclusion of results from the progression free survival and objective response rate for the indication of chronic lymphocytic leukemia based on the Idela + rituximab treatment. (b) (4)

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

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/s/

SIRISHA L MUSHTI
05/21/2014

YUAN L SHEN
05/21/2014

THOMAS E GWISE
05/21/2014

NDA/BLA Number: **Applicant: Gilead** **Stamp Date: 12/06/2013**

NDA 206545

Drug Name: Idelalisib(Idela) **NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF: No

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____√____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

NA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.			√	The analysis methods used in the analysis are not novel.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

File name: 5_Statistics Filing Checklist for a NDA 206545

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/s/

YUAN L SHEN
01/29/2014

THOMAS E GWISE
01/29/2014