EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 February 2018
EMA/202018/2018
Committee for Medicinal Products for Human use (CHMP)

Assessment report

Zydelig

International non-proprietary name: idelalisib

Procedure No. EMEA/H/C/003843/II/0032/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment Timetable

Timetable	Planned dates	Actual dates
Start of procedure:	18 February 2017	18 February 2017
CHMP Co-Rapporteur Assessment Report	12 April 2017	13 April 2017
CHMP Rapporteur Assessment Report	12 April 2017	12 April 2017
PRAC Rapporteur Assessment Report	21 April 2017	19 April 2017
PRAC members comments	26 April 2017	28 April 2017
Updated PRAC Rapporteur Assessment Report	27 April 2017	n/a
PRAC Outcome	5 May 2017	5 May 2017
CHMP members comments	8 May 2017	8 May 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 May 2017	12 May 2017
Request for Supplementary Information	18 May 2017	18 May 2017
Submission deadline	8 September 2017	8 September 2017
Re-start of procedure:	11 September 2017	11 September 2017
CHMP Rapporteur Assessment Report	10 October 2017	10 October 2017
PRAC Rapporteur Assessment Report	13 October 2017	11 October 2017
PRAC members comments	18 October 2017	18 October 2017
Updated PRAC Rapporteur Assessment Report	19 October 2017	20 October 2017
PRAC Outcome	26 October 2017	26 October 2017
CHMP members comments	30 October 2017	23 October 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2017	3 November 2017
Request for Supplementary Information (RSI)	9 November 2017	9 November 2017
Submission deadline	30 January 2018	30 January 2018
Re-start of procedure:	31 January 2018	31 January 2018
CHMP Rapporteur Assessment Report	7 February 2018	n/a
PRAC Rapporteur Assessment Report	7 February 2018	n/a
CHMP members comments	12 February 2018	n/a

Timetable	Planned dates	Actual dates
PRAC members comments	12 February 2018	n/a
Updated CHMP Rapporteur Assessment Report	15 February 2018	15 February 2018
Updated PRAC Rapporteur Assessment Report	15 February 2018	n/a
Opinion	22 February 2018	22 February 2018

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
B	bendamustine
BCR	B-cell receptor
BID	twice daily
BOR	best overall response
BR	bendamustine and rituximab
CI	confidence interval
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CR	complete response
CRi	complete response with incomplete marrow recovery
CSR	clinical study report
CYP3A	cytochrome P450 3A
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DOR	duration of response
EC	European Commission
EDC	electronic data capture
ESMO	European Society for Medical Oncology
EWB	emotional well-being
F	fludarabine
FAS	full analysis set
FDA	Food and Drug Administration
FCR	fludarabine, cyclophosphamide, and rituximab
FR	fludarabine and rituximab
FWB	functional well-being
HL	Hodgkin lymphoma
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	hazard ratio
HRQL	health-related quality of life
IDL	idelalisib (Zydelig®)
IGHV	immunoglobulin heavy chain variable region gene
iNHL	indolent non-Hodgkin lymphoma
IRC	independent review committee
ISE	integrated summary of efficacy
ISS	integrated summary of safety

ITT	intent to treat
IV	intravenously
KM	Kaplan-Meier
LNR	lymph node response
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MM	multiple myeloma
MST	Medical Search Term
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NE	not evaluable
NEst	not estimable
NR	not reached
O	ofatumumab
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetics
Pl	placebo
PML	progressive multifocal leukoencephalopathy
PR	partial response
PT	preferred term
Q1	first quartile
Q3	third quartile
R	rituximab
RCh	rituximab and chlorambucil
RL	rituximab and lenalidomide
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	system organ class
SPD	sum of the products of the greatest perpendicular diameters
SWB	social well-being
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd submitted to the European Medicines Agency on 31 January 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6. Extension of Indication: Extension of the approved chronic lymphocytic leukemia (CLL) indication for Zydelig to include its use in combination with bendamustine and rituximab based on the results of the primary analysis of pivotal Study GS-US-312-0115 "a Phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukemia" as a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 2.2 has also been submitted.

C.I.13: Submission of the final report from study 101-08, a phase 2, single-arm study evaluated idelalisib monotherapy and in combination with rituximab in elderly subjects with previously untreated CLL or small lymphocytic lymphoma. Inclusion of this report provides additional safety data to support the evaluation of the use of idelalisib in patients with CLL. Submission of this report is also made in fulfilment of PAM008.

C.I.13: Submission of the final report from study GS-US-312-0123, a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab in subjects with previously untreated CLL. Inclusion of this report is supportive of a complete safety evaluation concerning the use of this combination in patients with CLL.

The group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Zydelig (idelalisib [IDL]) is a competitive inhibitor of the adenosine triphosphate binding site of the phosphatidylinositol 3 kinase p110δ (PI3Kδ) catalytic domain.

On 18 September 2014, the European Commission (EC) approved Zydelig for use in combination with rituximab for the treatment of adult patients with CLL who have received at least 1 prior therapy, and as first-line treatment for patients with CLL with genetic mutations (chromosome 17p13.1 deletion [17p deletion] and/or TP53 mutation) who are unsuitable for chemo-immunotherapy.

The first-line indication was later modified following the conclusion of an Article 20 procedure to include only those patients with CLL and 17p deletion or TP53 mutation who are not eligible for any other therapies.

The Article 20 procedure was initiated due to an increased early fatality rate in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125.

Incidence of deaths, fatal AEs and SAEs in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

	GS-US-312-0123 (1st line CLL)		GS-US-313-0125 (iNHL with median of 2 prior therapies)		GS-US-313-0124 (iNHL with median of 1 prior therapy)	
	Idelalisib + BR (n = 156)	Placebo + BR (n = 154)	Idelalisib + BR (n = 318)	Placebo + BR (n = 155)	Idelalisib + R (n = 190)	Placebo + R (n = 93)
All Deaths	8%	3%	8%	6%	5%	1%
AE leading to death	8%	2%	6%	3%	4%	0%
SAEs	71%	42%	72%	35%	48%	10%

BR = bendamustine plus rituximab, R = rituximab

These studies were terminated early and the article 20 procedure resulted in a minor change in the approved indications (see above) and amendments to the SPC essentially focused on measures to reduce the risk for infections, especially the risk for opportunistic infections (pneumocystis and CMV).

The main underlying reasons for the unfavourable (early) benefit/risk in the studies referred to above were considered to be: The favourable prognosis of the enrolled patients, the favourable risk profiles of the control regimens and the add-on immune-toxicity of IDL, especially in relation to bendamustine + rituximab (BR).

Applications were subsequently filed to support the use of IDL in combination with ofatumumab (O) in patients with CLL based on the results of the Phase 3 Study GS-US-312-0119.

The present group of variations consist of:

- A variation application under C.I.6 proposing to expand the CLL indication for IDL to include its use in combination with bendamustine and rituximab (BR) based on the results of the primary analysis of pivotal Study GS-US-312-0115, entitled "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia."
- The submission – under the scope of C.I.13 - of the final report from study 101-08, a phase 2, single-arm study evaluated idelalisib monotherapy and in combination with rituximab in elderly subjects with previously untreated CLL or small lymphocytic lymphoma. Inclusion of this report provides additional safety data to support the evaluation of the use of idelalisib in patients with CLL. This submission is also made in fulfilment of PAM008 of the MA.
- The submission – under the scope of C.I.13 - of the final report from study GS-US-312-0123, a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab in subjects with previously untreated CLL. Inclusion of this report is supportive of a complete safety evaluation concerning the use of this combination in patients with CLL.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

This Type II variation for Zydelig includes the interim analysis of the pivotal Study GS-US-312-0115, entitled "A Phase 3, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS 1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia." The data contained herein support expansion of the Zydelig CLL indication statement with the addition of the following:

Zydelig is indicated in combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received at least one prior therapy.

An Environmental Risk Assessment (ERA) for Zydelig was included within the initial Marketing Authorisation Application. This assessment covered the use of Zydelig for the treatment of adult patients with indolent non-Hodgkin lymphoma refractory to rituximab and an alkylating agent and relapsed chronic lymphocytic leukemia. On 08 December 2015, a type IB variation was submitted to provide an updated environmental risk assessment for idelalisib with a Phase II assessment, as agreed during the initial Marketing Authorisation Application and detailed in the cumulative letter of recommendations.

The EMA guideline "Guideline on the environmental risk assessment of medicinal products for human use" [EMEA/CHMP/SWP/4447/00 corr 2] states that "the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g., a new indication may result in a significant increase in the extent of use." Accordingly, a revised ERA is not submitted in the context of this variation as the proposed revision to the approved CLL indication is for a new combination within the currently approved patient populations. It is not anticipated that there would be a significant increase in the extent of use.

Comment

The lack of an updated ERA is acceptable.

MS comment from *{confidential information deleted}*:

"We agree with the rapporteur and have an additional comment. The applicant acknowledged the submission of a phase II environmental risk assessment in the marketing authorisation procedure Zydelig EMEA/H/C/3843. The submission was announced for the fourth quarter of 2015. OMS {confidential information deleted} would appreciate to receive the announced updated environmental risk assessment including the study reports by the applicant or by the rapporteur."

Rapp comment on *{confidential information deleted}* MS comment;

The requested updated environmental risk assessment and study reports have been submitted by the MAH as part of a type IB variation, which was submitted in the q4 2015 (EMEA/H/C/3843/IB/20). Consequently, the information requested by *{confidential information deleted}* is available in the mentioned application. Since the updated ERA was submitted as a type IB variation it was approved via CHMP silent adoption and consequently no CHMP AR were produced. No MS comments were received in regard to the type IB variation. Since the studies have been approved and since they were not submitted as part of this application they cannot be re-assessed or requested. Hence, the request from *{confidential information deleted}* is not agreed upon.

Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. The ERA has not been updated since the context of this variation as the proposed revision to the approved CLL indication is for a new combination within the currently approved patient populations. Consequently, it is not anticipated that there would be a significant increase in the extent of use.

2.2.2. Conclusion on the non-clinical aspects

There are no non-clinical objections to this application.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of idelalisib.

2.3. Clinical aspects

2.3.1. C.I.13: Submission of the final report from study GS-US-312-0123.

Study 312-0123 was a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab (IDL+BR) vs. Pl+BR in subjects with previously untreated CLL.

This study was terminated early due to a safety signal (EPAR EMEA/H/A-20/1439/C/003843/0023, July 2016, article 20 procedure). Because the factors contributing to the AEs were not completely understood, the decision was made to terminate this study. Due to early study termination, the prespecified efficacy analyses were not conducted.

Issues discussed in the article 20 procedure included whether the side effects of IDL+BR were exaggerated in patients with treatment naïve CLL vs. treatment experienced , i.e. that the apparently unfavourable B/R first-line was not only related to the slow progression rate in the control (BR) arm. Therefore this AR is focused on safety.

Safety

IDL/Placebo Exposure (Safety Analysis Set)

	IDL + BR (N = 156)	Placebo + BR (N = 154)
Duration of Exposure to IDL (months)[a]		
N	156	154
Mean (StD)	9.7 (6.23)	13.5 (4.48)
Median	12.1	14.5
Q1, Q3	3.1, 15.0	12.2, 16.6
Min, Max	0.2, 22.1	0.3, 21.8
Cumulative Exposure to IDL, n (%)		
≥ 1 day	156 (100.0%)	154 (100.0%)
≥ 2 months	123 (78.8%)	147 (95.5%)
≥ 4 months	111 (71.2%)	145 (94.2%)
≥ 6 months	102 (65.4%)	140 (90.9%)
≥ 12 months	79 (50.6%)	123 (79.9%)
≥ 18 months	10 (6.4%)	16 (10.4%)
≥ 24 months	0	0
≥ 30 months	0	0
≥ 36 months	0	0

BR = bendamustine + rituximab, IDL = idelalisib, Q1 = first quartile, Q3 = third quartile; StD = standard deviation
a Duration of exposure for IDL (months) = ([last IDL/placebo dosing date – first IDL/placebo dosing date + 1)/ 30.4375.
The Safety Analysis Set included all subjects who receive ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.

Comment: Note the major difference in cumulative exposure already after 2 months. This is of course also reflected in the cumulative number of doses.

Cumulative Number of Doses		
≥ 1	156 (100.0%)	154 (100.0%)
≥ 2	156 (100.0%)	154 (100.0%)
≥ 4	141 (90.4%)	150 (97.4%)
≥ 6	122 (78.2%)	146 (94.8%)
≥ 8	111 (71.2)	141 (91.6)
≥ 10	95 (60.9)	133 (86.4)
≥ 12	77 (49.4)	119 (77.3)
≥ 14	1 (0.6)	0

Overall Summary of Adverse Events (Safety Analysis Set)

Adverse Event Category, n (%)	IDL + BR (N = 156)	Pl + BR (N = 154)
Any AE	156 (100.0)	153 (99.4)
IDL/Pl-Related AE	139 (89.1)	110 (71.4)
Rituximab-Related AE	124 (79.5)	115 (74.7)
Bendamustine-Related AE	140 (89.7)	140 (90.9)
≥ Grade 3 AE	150 (96.2)	124 (80.5)
≥ Grade 3 IDL/Pl-Related AE	122 (78.2)	59 (38.3)
≥ Grade 3 Rituximab-Related AE	93 (59.6)	68 (44.2)
≥ Grade 3 Bendamustine-Related AE	121 (77.6)	85 (55.2)
Any SAE	113 (72.4)	68 (44.2)
IDL/Pl-Related SAE	72 (46.2)	30 (19.5)
Rituximab-Related SAE	54 (34.6)	34 (22.1)
Bendamustine-Related SAE	76 (48.7)	32 (20.8)
AE Leading to IDL/Pl Dose Reduction	16 (10.3)	14 (9.1)
AE Leading to IDL/Pl Dose Interruption	115 (73.7)	68 (44.2)
AE Leading to IDL/Pl Discontinuation	60 (38.5)	12 (7.8)
AE Leading to Death	12 (7.7)	3 (1.9)

AE = adverse event; BR = bendamustine + rituximab; IDL = idelalisib; Pl = placebo; SAE = serious adverse event
Relationship to study drug is determined by investigator; AEs with missing relationships were considered to be related.
The Safety Analysis Set included all subjects who receive ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.

Comment: The investigators better differentiates IDL from Pl when it comes to higher grade AE/SAE/discontinuations. This expected for some of the events, such as colitis and transaminitis.

Adverse Events with ≥ 4% Difference in the IDL + BR Group when Compared to the Placebo + BR Group by MedDRA PT (Safety Analysis Set)

Preferred Term, n (%)	IDL + BR (N = 156)	Placebo + BR (N = 154)	Difference (%)
Number (%) of Subjects with Any AE with ≥ 2% Difference between Two Groups	156 (100.0)	151 (98.1)	
Pyrexia	87 (55.8)	52 (33.8)	22.0
Rash	64 (41.0)	34 (22.1)	18.9
ALT Increased	23 (14.7)	3 (1.9)	12.8
Hypokalaemia	25 (16.0)	5 (3.2)	12.8
Diarrhoea	66 (42.3)	46 (29.9)	12.4
Rash maculo-papular	31 (19.9)	12 (7.8)	12.1
AST increased	20 (12.8)	2 (1.3)	11.5
Febrile neutropenia	33 (21.2)	16 (10.4)	10.8
Weight decreased	19 (12.2)	4 (2.6)	9.6
Anemia	45 (28.8)	30 (19.5)	9.4
Mucosal Inflammation	15 (9.6)	1 (0.6)	9.0
Asthenia	22 (14.1)	9 (5.8)	8.3
Vomiting	37 (23.7)	24 (15.6)	8.1
Dehydration	14 (9.0)	3 (1.9)	7.0
Pneumonia	20 (12.8)	9 (5.8)	7.0
Urinary Tract Infection	18 (11.5)	7 (4.5)	7.0
Dyspnoea	24 (15.4)	13 (8.4)	6.9
Dry Skin	14 (9.0)	4 (2.6)	6.4
Hypophosphatemia	9 (5.8)	0	5.8
Dry Mouth	11 (7.1)	4 (2.6)	4.5
Sepsis	9 (5.8)	2 (1.3)	4.5
Transaminase Increased	7 (4.5)	0	4.5
Chills	21 (13.5)	14 (9.1)	4.4

Comment: There are major differences between study arms, also in summary measures such as weight decrease (12 vs. 3%) and dehydration (9 vs. 2%).

Deaths: There were more deaths in the IDL+BR arm: 12 /7.7%) vs. 3 (1.9%), thereof infectious events 8 vs. 1.

SAEs Reported for ≥ 2% of Subjects in Either Treatment Group (Safety Analysis Set)

Preferred Term, n (%)	IDL + BR (N = 156)	Placebo + BR (N = 154)
Number of Subjects (%) with any SAE	113 (72.4)	68 (44.2)
Febrile Neutropenia	29 (18.6)	16 (10.4)
Pyrexia	26 (16.7)	19 (12.3)
Pneumonia	11 (7.1)	6 (3.9)
Sepsis	9 (5.8)	2 (1.3)
Anemia	8 (5.1)	2 (1.3)
Neutropenia	7 (4.5)	1 (0.6)
Diarrhoea	6 (3.8)	1 (0.6)
Neutropenic Sepsis	5 (3.2)	1 (0.6)
Pneumonitis	5 (3.2)	3 (1.9)
Tumour Lysis Syndrome	5 (3.2)	4 (2.6)
Atrial Fibrillation	4 (2.6)	3 (1.9)
Rash	4 (2.6)	1 (0.6)
Urinary Tract Infection	4 (2.6)	1 (0.6)

BR = bendamustine + rituximab, IDL = idelalisib, Pl = placebo, SAE = serious adverse event
The Safety Analysis Set includes all subjects who receive ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
AEs were classified by PT using MedDRA version 19.0.
Multiple AEs were counted only once per subject for each SOC and PT.

Comment: Infectious events dominate.

Study drug discontinuation: Altogether 60 (39%) vs. 12 (8%) discontinued study drug, IDL vs. Pl.

Treatment-Emergent Transaminase Elevations (Safety Analysis Set)

	IDL + BR (N = 156) n (%)	Pl + BR (N = 154) n (%)
Subjects with any Grade 3 or 4 ALT or AST Elevation	41 (26.3)	2 (1.3)
Subjects with any Grade 3 or 4 ALT Elevation	41 (26.3)	2 (1.3)
Subjects with any Grade 3 or 4 AST Elevation	26 (16.7)	2 (1.3)
Subjects with any Grade 3 or 4 ALT and AST Elevation	26 (16.7)	2 (1.3)
Resolved to Grade 1 or Less	39 (25.0)	2 (1.3)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BR = bendamustine + rituximab, IDL = idelalisib, Pl = placebo
The Safety Analysis Set includes all subjects who receive ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.

One subject in the IDL + BR group (subject [redacted]) and no subject in the placebo + BR group experienced AST or ALT > 3 × ULN with concurrent elevation of bilirubin > 2 × ULN **and** elevated (> 1.5 ULN) alkaline phosphatase.

Conclusions: A side by side comparison between studies 0123 and 0115 is warranted in order to try to understand whether "first-line" is a risk factor per se for IDL add-on toxicity.

Obviously patients are selected for inclusion in study 0115 based on tolerability to prior therapy. Here, however, the BR arms may serve as "normalizer". Due to major differences in time of exposure, data per 2 months period could provide easier to interpret data.

2.3.2. Final study report Study 101-08 (PAM008)

(from overview 2014)

A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of idelalisib in Combination with Rituximab in Elderly Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (interim analysis)

A total of 5 sites in the United States (US) participated in this study

First subject screened: 28-SEP-2010

Last subject observation: 22-MAR-2013

Eligibility

Patients ≥ 65 years with CLL or SLL Binet Stage C or Rai Stage III or IV or active and symptomatic disease and World Health Organization (WHO) performance status of ≤ 2. Patients should have had no prior therapy for CLL or SLL, except corticosteroids for symptom relief

Experimental/treatment

All subjects received idelalisib 150 mg BID orally on Days 1 through 28 of each 28-day cycle for 48 weeks and rituximab 375 mg/m2 intravenously weekly for 8 doses (Cycles 1 and 2). Subjects completing Protocol 101-08 with a clinical response following 48 weeks of idelalisib treatment were eligible to continue the treatment under a long-term extension protocol (101-99).

Primary endpoint: ORR. A result of 70% ORR with the addition of idelalisib to rituximab was considered to be clinically meaningful for this study.

The mean and median age was about 71-72 years with a range from 65 to 90. Altogether 1/3 patients did not complete 48 weeks of therapy thereof none for disease progression, but 17/64 for AEs.

Of high-risk criteria, unmutated IGHV was present in a majority (58%) of the subjects, whereas only 14 % were positive for TP53 Mutation/del (17p).

Results

Table 1: Overall Response Rate (ITT Analysis Set)

	IDELA + Rituximab (N = 64) n (%)				
	Total	17p-/TP53 Mutation[a]		IGHV Mutation[a]	
Best Overall Response	(N = 64)	Either (N = 9)	Neither (N = 52)	Mutated (N = 23)	Unmutated (N = 37)
Complete Response	9 (14.1)	3 (33.3)	4 (7.7)	5 (21.7)	2 (5.4)
Partial Response	53 (82.8)	6 (66.7)	46 (88.5)	17 (73.9)	34 (91.9)
Stable Disease	0	0	0	0	0
Progressive Disease	0	0	0	0	0
Not Evaluable	0	0	0	0	0
Not Done[b]	2 (3.1)	0	2 (3.8)	1 (4.3)	1 (2.7)
Overall Response Rate[c]	62 (96.9)	9 (100.0)	50 (96.2)	22 (95.7)	36 (97.3)
95% CI[d]	89.2 – 99.6	66.4 – 100	86.8 – 99.5	78.1 – 99.9	85.8 – 99.9

The overall response rate of 97% is very high and included in this first-line elderly population CR in about 14%. No subjects had a relapse while on the study.

Forty-nine of 50 subjects (98%) had lymph node response. Two subjects for whom the response assessment was "not done" had withdrawn from the study due to dose limiting toxicity (Grade 3 rash,

elevated ALT and AST and Grade 3 rash, respectively). The CR rate of 14 % indicates that BM biopsies showed remaining tumour infiltration. After a median follow-up of 14+ months, PFS data are immature, but there are no events of PD.

Update

- 07 June 2016 (Last Subject Observation) 21 April 2016 (Last Subject Observation for the Primary Endpoint)

The results of the second of two cohorts (IDL alone) are now reported. Results in the IDL + rituximab cohort were reported above.

In **Cohort 2**, eligible subjects received IDL 150 mg orally twice daily on Days 1 through 28 of each 28-day cycle. Subjects were evaluated for response after Weeks 8, 16, 24, and every 12 weeks thereafter according to modified standard criteria.

Cohort 2 was terminated early in March 2016 due to a safety signal demonstrating increased rates of deaths and serious adverse events (SAEs), generally due to infections, in a pooled analysis conducted by an independent Data Monitoring Committee (DMC) during regular review of 3 Phase 3 studies (GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125) evaluating the addition of IDL to standard therapies in first-line CLL or early-line relapsed indolent non-Hodgkin lymphoma (iNHL). Subsequently, a decision was made to terminate all ongoing studies treating first-line CLL and early-line iNHL populations, which included Cohort 2 of Study 101-08.

Efficacy: Partial responses were seen in 36 subjects (87.8%) in Cohort 2, including 5 of 6 subjects with 17p deletion and/or TP53 mutation. The KM estimate of median DOR was 22.5 months and median PFS was 26.2 months.

Safety: The most common AEs were diarrhoea (28 subjects, 68.3%); nausea, pyrexia, and rash (14 subjects, 34.1%, each); and fatigue (13 subjects, 31.7%).

The most common AEs of **≥ Grade 3** severity were diarrhoea (11 subjects, 26.8%), ALT increased (9 subjects, 22.0%), and AST increased (7 subjects, 17.1%).

Altogether 8 subjects (19.5%) had ≥ Grade 3 **infections**. The median time to onset of the first ≥ Grade 3 infection was 24.8 weeks (range: 4.9 to 35.7 weeks). Three subjects permanently discontinued IDL due to infections, including Grade 3 cellulitis (2 subjects) and Grade 5 pneumonia (1 subject; this event led to the subject's death). No subject had a ≥ Grade 3 AE of febrile neutropenia during the study.

Fifteen subjects (36.6%) had ≥ Grade 3 AEs of diarrhea/colitis (14 subjects with Grade 3 and 1 subject with Grade 4 events). The median time to onset of the first ≥ Grade 3 event of diarrhoea/colitis (n = 15) was 33.4 weeks (range: 6.1 to 92 weeks), and the median time to resolution of any ≥ Grade 3 diarrhea/colitis (n = 14) was 1.5 weeks (range: 0.9 to 9.0 weeks). Nine subjects (22.0%) permanently discontinued IDL due to ≥ Grade 3 diarrhea or colitis.

Conclusions: Also monotherapy may seem rather poorly tolerated in elderly treatment naïve CLL patients not assumed to tolerate chemotherapy (22% discontinued due to diarrhea/colitis). This, however, should be put in context of durable activity, median PFS > 2 years. Infectious events and causality are hard to assess in the absence of a control group. Monotherapy is clearly very active.

PAM008 is fulfilled.

2.3.3. C.I.6. Extension of Indication pivotal Study GS-US-312-0115

2.3.3.1. Introduction

GCP: The Clinical trials were performed in accordance with GCP as claimed by the applicant

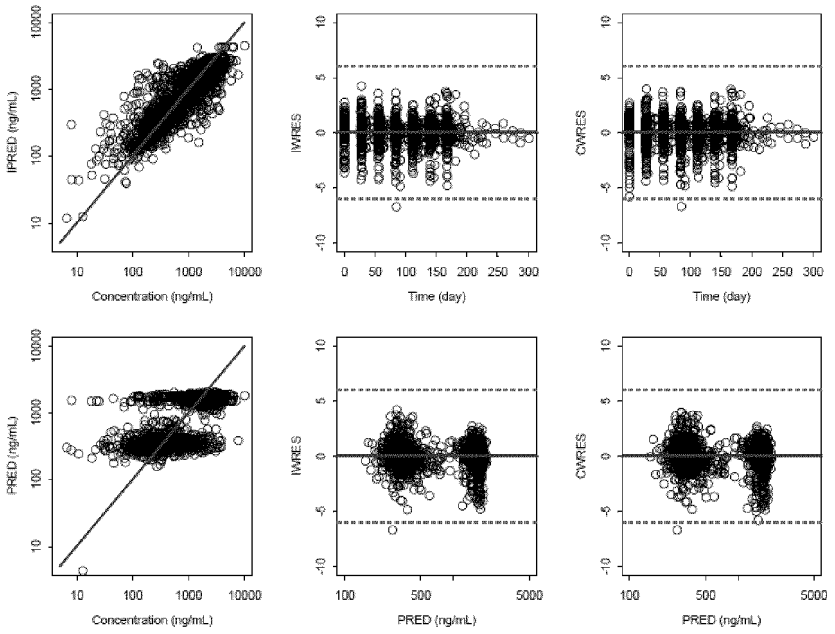
2.3.3.2. Pharmacokinetics

Population-PK GS-US-312-0115
A population pharmacokinetic (popPK) model has previously been developed in NONMEM7 for idelalisib based on data from 10 clinical trials (101-01, 101-02, 101-04, 101-05, 101-06, 101-07, 101-08, 101-09, 101-11, and 339-0101). The final model structure was a 2-compartment model with a first-order absorption rate constant and absorption lag time. A popPK model for metabolite GS-563117 based on 6 studie (101-02, 101-05, 101-08, 101-09, 101-11, and 339-0101) has also been developed.

An external validation using PK data from phase 3 study GS-US-312-0115 and the final popPK model for idelalisib and GS-563117 was conducted The plasma concentration data for 207 CLL patients in study GS-US-312-0115 (Idelalisib 150 mg BID in combination with BR) were measured using the same assay as was used for the studies in the model development dataset. The target population comprises adults with previously treated CLL who have measurable lymphadenopathy, require treatment for CLL, have received prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody; are not refractory to bendamustine; have experienced CLL progression <36 months since the completion of the last prior therapy; and are currently sufficiently fit to receive cytotoxic therapy, and randomized in a 1:1 ratio to receive either idelalisib/bendamustine/rituximab combination therapy (Arm A) or bendamustine/rituximab combination therapy (Arm B).

Predicted idelalisib and GS-563117 plasma concentrations for validation patients were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the final model. The predicted IDELA /GS-563117 concentrations (PRED) were compared with the corresponding observed IDELA/GS-563117 concentrations (DV) as well as the individual weighted residuals (IWRES) or CWRES versus PRED or time.

The general goodness-of-fit plots for the IDELA external validation patients

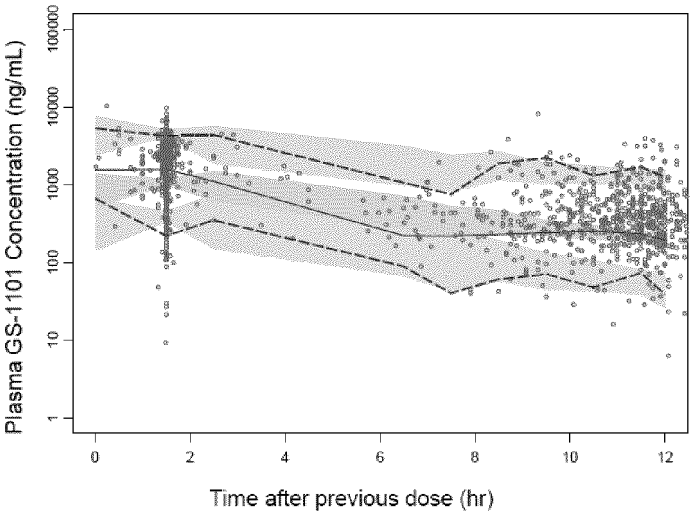


Left: Individual predicted (IPRED) plasma IDELA concentrations versus observed IDELA concentrations (upper) and population predicted (PRED) plasma IDELA concentrations versus observed plasma IDELA concentrations (lower). Middle: individual weighted residuals (IWRES) versus time (upper) and conditional weighted residuals (CWRES) versus time (lower). Right: IWRES versus PRED (upper) and CWRES versus PRED (lower). Points are individual data. Red solid lines represent the unit diagonal (left) or line at zero (middle and right). Blue dashed lines represent |CWRES| of 6.

The previously developed model was used to create a prediction corrected visual predictive check (pcVPC) using the parameter estimates from the previous model to show the time course of the predicted mean and spread of concentrations (5th to 95th percentile) versus the new observed data.

Figure 1.

Prediction-corrected VPC of IDELA plasma concentration versus time-after-previous-dose for validation patients



Points are the observed plasma IDELA concentrations, solid red lines represent the median observed value, and dashed lines represent 5th percentile and 95th percentiles of the observed values. Blue shaded areas represent the spread of the median predicted values (5th to 95th percentile), and red shaded areas represent the spread (5th percentile and 95th percentile) of the 5th and 95th predicted percentile concentrations.

The MAH concluded that a good agreement between the predicted concentrations and the observed concentrations was observed in the GOF plots and no bias was observed over time and across predicted concentrations. Further, the MAH determined that the pcVPC plots show that the model adequately describes the central tendency and the spread of the observed PK concentrations.

The impact of type of cancer/background treatment, age, gender, race, body weight, baseline CLcr, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were tested. The MAH concluded that none of the intrinsic factors evaluated affected idelalisib exposures, consistent with previous data.

Table 2. shows parameter estimates for CL/F, Q/F, Vc/F and Vp/F to be compared with previously reported in subjects with hematologic malignancies of 14.9 L/h, 11.8 L/h, 22.7 L, and 73.0 L for idelalisib, and 4.39 L/h,1.28 L/h, 7.54 L, and 16.1 L for GS-563117 (for CL/F, Q/F, Vc/F and Vp/F respectively). Table 3. shows idelalisib exposures from study GS-US-312-0115 (idelalisib with background treatment) and for study 101-02 (idelalisib monotheraphy).

Table 2.

IDL and GS-563117 Population PK Parameters in Study GS-US-312-0115

Parameter Description	Parameter Estimates Median (5^{th} – 95^{th} Percentile) Study GS-US-312-0115 (N = 207)
IDL	
Apparent Oral Clearance, CL/F (L/hr)	14.3 (8.50 – 23.4)
Apparent Inter-Compartmental Clearance, Q/F (L/hr)	11.6 (8.70 – 14.3)
Apparent Central Volume, V_c/F (L)	19.4 (12.5 – 83.9)
Apparent Peripheral Volume, V_p/F (L)	70.3 (40.3 – 108.3)
GS-563117	
Apparent Oral Clearance, CL/F (L/hr)	3.99 (1.91 – 10.2)
Apparent Inter-Compartmental Clearance, Q/F (L/hr)	1.28 (1.23 – 1.32)
Apparent Central Volume, V_c/F (L)	7.51 (4.77 – 13.1)
Apparent Peripheral Volume, V_p/F (L)	16.1 (15.5 – 16.6)

Source: QP 2016-1001

Table 3.

IDL Exposures in Combination with Background Treatment versus Monotherapy Across Disease Indication (PK Analysis Sets)

IDL PK, Mean (%CV)	IDL + BR (Study GS-US-312-0115; R/R CLL) (N = 207)	IDL Monotherapy[a] (101-02; CLL/NHL) (N = 61)
AUC_{tau} (ng•h/mL)	10,811.7 (33.5)[b]	10,598.1 (40.8)
C_{max} (ng/mL)	1959.7 (31.4)	1861.4 (43.3)
C_{tau} (ng/mL)	372.8 (60.9)	381.3 (57.9)

The PK analysis set included subjects in the Safety Analysis Set who had baseline and on-study measurements to provide interpretable results, with treatment group designated according to the actual treatment received.

a Subjects in Study 101-02 with CLL, non-Hodgkin lymphoma, acute myeloid leukemia, or multiple myeloma who received IDL 150 mg twice daily monotherapy are included

b AUC_{tau} represents half the AUC_{0-24} values shown in the source table.

Comment

The previously developed model was used for external validation of new data from study GS-US-312-0115. This approach is reasonable to indicate that PK is similar to previous studies. However, the data should also have been pooled with previous data and the model should have been updated and covariate analysis and concomitant medication should have been tested as a covariate. From the popPK report, this does not appear to have been conducted but in the clinical summary, updated parameters such as CL/F can be found. Further, PK in the two different study arms, idelalisib/bendamustine/rituximab combination therapy (Arm A) or bendamustine/rituximab combination therapy (Arm B), should have been compared.

The table showing new parameters was found in the clinical summary report and popPK modeling report was listed as reference, however the assessors are unable to find the table in the popPK report. The results do indicate similar PK also for CLL patients. However it is again not clear if there may be a difference between arm A and arm B.

It is not agreed that no bias was observed over time and across predicted concentrations, there appears to be a clear trend in PRED vs. DV plot and trends can be seen also in the VPC.

Population-PK 312-0123 and 313-0124 and 313-0125

Similarly to external validation described above, external validation was conducted for Phase 3 studies GS-US-312-0123 (IDELA +bendamustine/rituximab in untreated CLL), GS-US-313-0124 (IDELA + rituximab in relapsed/refractory iNHL), and GS-US-313-0125 (IDELA + bendamustine/rituximab in relapsed/refractory iNHL). As before, the previously developed model was used. Predicted idelalisib and GS-563117 plasma concentrations for validation patients were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the final model. The previously developed model was used to create a prediction corrected visual predictive check.

Comment

The patient population in studies GS-US 312-0123 (untreated CLL), 313-0124/313-0125 (R/R iNHL) does not represent the patient population in this procedure (previously treated CLL patients) and therefor the value of the PK information from 312-0123 and 313-0124 and 313-0125 is limited for this procedure.

Similar issues as for popPK analysis for study GS-US-312-0115 are seen in this popPK analysis. The dataset and popPK model should have been updated and some clear model misspecification can be seen in the VPCs.

AUC, Cmax and Ctau were presented for the 3 different studies using individual model parameters. The VPCs and the calculated AUC, Cmax and Ctau indicate that PK appears to be fairly similar between the 3 studies.

Drug drug interaction

DDI for the new proposed combination

There is a lack of discussion about potential DDI between idelalisib/bendamustine/rituximab by the MAH. The idelalisib and rituximab combination is already approved but bendamustine potential for DDI with idelalisib should be discussed by the MAH.

Comment

In the GS-US-312-0115 study, 2 arms were studied, one with idelalisib/bendamustine/rituximab and the other with idelalisib/rituximab. Thus, a general discussion on potential DDI of Bendamustine with idelalisib or rituximab, supported by a presentation of the pharmacokinetics (PK) from the 2 different arms is desired and should be provided by the MAH.

Cyp3A4 substrates

GS-563117, the primary oxidative metabolite of IDL, is a strong time-dependent CYP3A inhibitor. Coadministration of IDL, 150 mg twice daily, increased the exposure to a single, 5 mg, oral dose of midazolam (Cmax increased 2.4-fold and AUC increased 5.4-fold). The MAH proposes to change the language in Section 7.2 to: "Avoid coadministration of Zydelig with sensitive or narrow therapeutic index CYP3A substrates (e.g., pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam)." This recommendation seeks to balance the significant therapeutic need for the use of co-medications and is consistent with the original FDA Clinical Pharmacology division review comments.

Comment

Acceptable from a clinical perspective.

2.3.3.3. PK/PD modelling

No full PK/PD modelling report can be found, only a report with PK/PD tables/figures which cannot be fully assessed due to lack of information on how they were produced. In the clinical summary, exposure/ response and safety/response is dicussed. Exposure/safety response analysis were conducted using exposures derived from the popPK model. The efficacy metrics used to evaluate the relationship included change in tumor size (sum of the products of the greatest perpendicular diameters [SPD] of index lesions), best overall response (BOR), duration of response (DOR), PFS, and lymph node response (LNR). The PK/PD relationship between IDL exposures and efficacy parameters is discussed in detail in. Studies GS-US-312-0123 (IDL + BR in untreated CLL), GS-US-313-0124 (IDL + R in relapsed/refractory iNHL), and GS-US-313-0125 (IDL + BR in relapsed/refractory iNHL) were terminated early and not included in the exposure-efficacy analysis.

Overall, IDL exposure-efficacy analyses using data from Study GS-US-312-0115 showed a lack of relationship between idelalisib exposure and various efficacy endpoints, indicating that idelalisib 150 mg twice in combination with BR produced robust and consistent therapeutic effects in subjects with relapsed/refractory CLL across the exposure range observed. The MAH points out that hese results are consistent with the results from exposure-efficacy analyses reported previously for subjects with CLL and iNHL.

Safety parameters that were assessed included laboratory abnormalities of AST and ALT and all Grade ≥ 3 AEs, including colitis, diarrhea, infection, neutropenia, pneumonia, pneumonitis, and skin rash for Study GS-US-312-0115 (table v), and infection and neutropenia for Studies GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125.

Study GS-US-312-0115: GS-563117 Exposures for Subjects Receiving IDL 150 mg Twice Daily in Combination with BR with Grade 3 or 4 Adverse Events

Mean (%CV)	Any AE Grade ≥ 3		Neutropenia Grade ≥ 3		Diarrhea Grade ≥ 3		Rash Grade ≥ 3		Infection Grade ≥ 3		Pneumonia Grade ≥ 3		Colitis Grade ≥ 3		Diarrhea/Colitis Grade ≥ 3		Pneumonitis Grade ≥ 3	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	194	13	151	56	19	188	13	194	80	127	24	183	2	205	21	186	3	204
C_{max} (ng/mL)	4076.9 (46.1)	3656.4 (41.7)	4051.5 (48.2)	4047.7 (39.2)	4208.3 (53.8)	4034.5 (45.1)	4163.0 (43.8)	4042.9 (46.1)	4533.2 (46.7)	3746.4 (43.0)	5083.0 (44.6)	3915.1 (45.0)	2458.5 (36.0)	4066.0 (45.7)	4041.7 (54.9)	4051.5 (44.9)	5926.1 (22.9)	4022.9 (46.1)
AUC_{0-24h} (ng•h/mL)	82023.2 (50.1)	71384.1 (42.9)	81725.4 (52.3)	80356.5 (42.5)	82157.1 (62.6)	81274.0 (48.6)	84998.0 (44.1)	81110.9 (50.3)	91443.6 (51.3)	75000.1 (46.3)	101914.3 (48.3)	78658.8 (49.1)	49808.4 (31.6)	81662.8 (49.7)	79076.2 (63.1)	81612.3 (48.4)	119360.8 (21.8)	80796.1 (50.1)

An increase in the incidence of Grade 3 or 4 AE of infections was observed with higher IDL exposures when administered in combination with BR. Similar results were observed for ≥ Grade 3 infections versus steady-state AUC0-24h. The median daily dose was identical between subjects with and without ≥ Grade 3 infections.

Comment

Full assessment of PK/PD modeling was not possible due to lack of a PK/PD modeling report. The results discussed in the clinical summary indicate a constant therapeutic effect.

An increase in the incidence of Grade 3 or 4 AEs of infections with higher idelalisib exposures was observed across studies. Similar results were observed for Grade ≥ 3 infections versus steady-state AUC0-24h.

2.3.3.4. Conclusions on clinical pharmacology

The following measures are considered necessary to address issues related to clinical pharmacology:

- A discussion on potential DDI of Bendamustine with idelalisib and rituximab, supported by a presentation of the pharmacokinetics from the 2 different arms in study GS-US-312-0115 should be provided by the MAH.

2.3.3.5. Clinical efficacy

Main study

Study GS-US-312-0115 is pivotal for this submission and was discussed in the article 20 procedure including survival data (not part of the publication "Idelalisib Plus Bendamustine and Rituximab (BR) Is Superior to BR Alone in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study, Zelenetz et al. Blood 2015). At that time available data were considered to be compatible with an acceptable risk.

- A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia.

Subjects were enrolled at total of 110 sites in the following countries: Australia, Belgium, Canada, Croatia, Czech Republic, France, Greece, Hungary, Ireland, Italy, New Zealand, Poland, Portugal, Romania, Russia, Spain, Turkey, United Kingdom, and United States.

Study Period: 15 June 2012 (First Subject Screened)

07 October 2015 (Last Subject Observation for the Primary Analysis)

02 May 2016 (Last Subject Observation for Follow-Up Assessments of Safety and Overall Survival [OS])

Methods

Randomisation: 1:1, fixed-block centralized randomization
Stratification: 17p deletion and/or TP53 mutation in CLL cells (either versus neither [or indeterminate]),

Immunoglobulin heavy chain variable region (IGHV) mutation (unmutated [or IGHV3-21] versus mutated [or indeterminate])

Disease status (refractory [CLL progression < 6 months from completion of prior therapy] versus relapsed [CLL progression ≥ 6 months from completion of prior therapy])

Treatments
Rituximab: 375 mg/m2 intravenously on Day 1 in the first cycle and 500 mg/m2 intravenously on Day 1 of each of the subsequent 5 cycles (6 cycles total; 4 weeks per cycle).

Bendamustine: 70 mg/m2/infusion; bendamustine was given on Days 1 and 2 of each of the 6 planned cycles.

Bendamustine and rituximab were administered until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable bendamustine- or rituximabrelated toxicity, pregnancy, substantial noncompliance with study procedures, study discontinuation, or a maximum of 6 cycles.

Idelalisib 150 mg taken orally (PO) twice daily (BID) or matching placebo PO BID was administered continuously until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation, even if bendamustine and/or rituximab were discontinued. The 150-mg dose was used for initial therapy; a 100 mg twice daily dose was administered in those subjects who required a dose reduction.

According to licensed dosages.

Study Procedures

Clinic/laboratory visits: every 2 weeks through Week 24 and every 6 weeks between Weeks 24 and 48, past Week 48 every 12 weeks. Subjects were assessed for safety at each clinic visit.

Subjects were assessed for CLL disease status by physical and laboratory examinations at each clinic visit and by computed tomography (CT) or magnetic resonance imaging (MRI) at Weeks 12, 24, 36, and 48 and every 12 weeks thereafter until definitive progression.

Main eligibility criteria

- Diagnosis of B-cell CLL, IWCLL criteria.
- CLL that warrants treatment (IWCLL)
- Measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by CT or MRI)
- Prior treatment for CLL comprising:

  ≥ 2 cycles of a regimen containing a purine analogue (eg, fludarabine, pentostatin, cladribine) or bendamustine, and

  ≥2 doses with a regimen containing an anti-CD20 monoclonal antibody (eg, rituximab, ofatumumab, obinutuzumab)
- Documentation of CLL progression < 36 months since the completion of the last prior therapy for CLL
- Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥ 3 weeks before randomization
- All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before randomization (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grades 1 or 2 permitted])
- Karnofsky performance status (KPS) score of ≥ 60

Outcomes/endpoints

Primary Endpoint:

PFS by IRC – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria other than lymphocytosis alone.

Secondary Endpoints:

By IRC: Overall response rate (ORR), lymph node response (LNR) rate, OS, and complete response (CR) rate (type 1 control).

For a **CR**, all of the following criteria were to be met:

- No evidence of new disease
- ALC in peripheral blood of < 4 x 109/L
- Regression of all index nodal masses to normal size ≤ 1.5 cm in the LD
- Normal spleen and liver size
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index diseas.e
- Morphologically negative bone marrow defined as < 30% of nucleated cells being lymphoid cells and no lymphoid nodules in a bone marrow sample that is normo-cellular for age.
- Peripheral blood counts meeting all of the following criteria: ANC > 1.5 x 109/L without need for exogenous growth factors. ANC values within 4 weeks postbaseline, within 2 weeks after granulocyte-colony stimulating factor (G-CSF) or within 4 weeks after Neulasta were excluded from the neutrophil response rate evaluation.

  Platelet count ≥ 100 x 109/L without need for exogenous growth factors. Platelet values within 4 weeks postbaseline or within 8 days after a transfusion were excluded from the platelet response rate evaluation.

  Hemoglobin ≥ 110 g/L (11.0 g/dL) without red blood cell transfusions or need for exogenous growth factors. Hemoglobin values within 4 weeks postbaseline, within 4 weeks of receiving packed cell/whole blood transfusion or within 6 weeks receiving exogenous growth factors (eg, Darbepoetin alfa) were excluded for the hemoglobin response evaluation.

"Patient Well-Being"

OS, change from baseline in HRQL domain and symptom scores based on FACT-Leu questionnaire, Changes from baseline in KPS (no type 1 error controil).

Long-term, follow-up

Follow-up for survival was conducted at approximately 6-month intervals for 5 years, starting at the end-of-study visit. Information gathered included medical status, antitumor treatments, secondary malignancies, and survival.

Statistical methods

Please refer to the reporting of endpoints.

Amendments: There were altogether 9 protocol amendments, December 2012 – October 2016. The study was opened was cross-over (a. 6, Dec 2015) but the possibility was removed in March 2016 due to safety concerns (article 20). Other amendments focused on updates on PK and DDI, safety clarifications. In no case these changes threatened the integrity of the trial.

Comment: The study is viewed as a standard-designed, add-on trial with proper background therapy for the line of therapy. Outcome measures are standard, but it is noticed that OS was not selected as a secondary endpoint (no protected alpha). This will not affect the reporting of OS data in the SPC, whilst HRQoL (no alpha protection) are not accepted for inclusion in the SPC.

Results

Disposition of Subjects with Respect to continuation on Study based on Data through 02 May 2016 (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)	Total (N = 416)
Subject Disposition	n (%)	n (%)	n (%)
Randomized	207 (100)	209 (100)	416 (100)
Randomized but Not Treated With Any Drug	0	0	0
Randomized but Not Treated With IDL/Placebo	0	1 (0.5)	1 (0.2)
Treated with Any Drug[b]	207 (100)	209 (100)	416 (100)
Ongoing in Study	70 (33.8)	23 (11.0)	93 (22.4)
Met Primary Study Endpoint[a]	73 (35.3)	142 (67.9)	215 (51.7)
Disease Progression	57 (27.5)	127 (60.8)	184 (44.2)
Death	16 (7.7)	15 (7.2)	31 (7.5)
Discontinued Study[a]	64 (30.9)	44 (21.1)	108 (26.0)
Adverse Event	27 (13.0)	13 (6.2)	40 (9.6)
Withdrawal by Subject	20 (9.7)	8 (3.8)	28 (6.7)
Physician Decision	7 (3.4)	19 (9.1)	26 (6.3)
Other	4 (1.9)	3 (1.4)	7 (1.7)
Noncompliance with Study Drug	3 (1.4)	0	3 (0.7)
Other Anticancer/Experimental Therapy	2 (1.0)	1 (0.5)	3 (0.7)
Lost to Follow-Up	1 (0.5)	0	1 (0.2)

BR = bendamustine + rituximab, IDL = idelalisib, Pl = placebo
a Reason for discontinuation as determined by the investigator
b Any drug refers to any protocol-specified drug, ie, bendamustine, rituximab, IDL, or placebo

Comment: There were more patients continuing on study in the experimental arm (34% vs. 11%). Reasons for discontinuing study showed clear differences, for example, for PFS 35% vs. 68%.

Conduct of the study

The most frequently reported important protocol deviation was not re-consenting the subject with a revised ICF at the first opportunity (33.3% of subjects in the IDL + BR group and 26.3% of subjects in the placebo+ BR group).

Important Protocol Deviations (ITT)

Protocol Deviation, n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)	Total (N = 416)
Number of Subjects with at Least 1 Important Protocol Deviation	109 (52.7)	89 (42.6)	198 (47.6)
Number of Subjects per Specific Deviation			
Informed Consent Form	69 (33.3)	55 (26.3)	124 (29.8)
Other	37 (17.9)	33 (15.8)	70 (9.6)
Eligibility Criteria	7 (3.4)	9 (4.3)	16 (3.8)
Other Treatment Compliance Issue	9 (4.3)	5 (2.4)	14 (3.4)
Treatment/Dosing Compliance	7 (3.4)	7 (3.3)	14 (3.4)
Excluded Concomitant Medication Received	2 (1.0)	2 (1.0)	4 (1.0)

Comment: Note that re-consenting was required in relation to the article 20 events.

Baseline data

Demographics: About ¾ of the patients were male, around 90% Caucasians, median=mean age about 63 years, KPS <70 in about 10%, 90 and above in about 60%.

CLL Disease History (ITT)

Disease Characteristic	IDL + BR (N = 207)	Pl + BR (N = 209)	Total (N = 416)
Time Since Diagnosis (years)[a]			
N	207	208	415
Mean (StD)	7.3 (4.50)	7.0 (4.27)	7.2 (4.38)
Median	6.2	6.3	6.2
Rai Stage at Screening, n (%)			
0	1 (0.5)	5 (2.4)	6 (1.4)
I	42 (20.3)	41 (19.6)	83 (20.0)
II	63 (30.4)	69 (33.0)	132 (31.7)
III	17 (8.2)	17 (8.1)	34 (8.2)
IV	82 (39.6)	70 (33.5)	152 (36.5)
Not Available	2 (1.0)	7 (3.3)	9 (2.2)
Binet Stage at Screening, n (%)			
A	18 (8.7)	26 (12.4)	44 (10.6)
B	87 (42.0)	89 (42.6)	176 (42.3)
C	98 (47.3)	89 (42.6)	187 (45.0)
Not Available	4 (1.9)	5 (2.4)	9 (2.2)

Comment: As expected for a next-line CLL study conducted in purine experienced patients with BR as study background therapy.

Subject Distribution by Stratification Factors (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)	Total (N = 416)
17p Deletion and/or TP53 Mutation Status			
17p Deletion and/or TP53 Mutation	69 (33.3)	68 (32.5)	137 (32.9)
Neither 17p Deletion nor TP53 Mutation	138 (66.7)	141 (67.5)	279 (67.1)
IGHV Mutation Status			
Mutated	34 (16.4)	36 (17.2)	70 (16.8)
Unmutated	173 (83.6)	173 (82.8)	346 (83.2)
Disease Status			
Refractory	70 (33.8)	68 (32.5)	138 (33.2)
Relapsed	137 (66.2)	141 (67.5)	278 (66.8)

The median (Q1, Q3) number of prior CLL regimens was 2.0 (1.0, 4.0) with a range of 1 to 13 prior regimens received. The most common prior regimens were fludarabine + cyclophosphamide + rituximab (66.8%; 278 subjects), fludarabine + cyclophosphamide (22.4%; 93 subjects), single-agent chlorambucil (18.0%; 75 subjects), and bendamustine + rituximab (11.3%, 47 subjects).

The median (Q1, Q3) time since last prior regimen was 18.1 (4.8, 26.9) months for subjects in the IDL + BR group and 13.9 (5.9, 27.2) months for subjects in the placebo + BR group.

Outcomes and estimation

Primary Endpoint: PFS by IRC Assessment, 07 October 2015 (ITT)

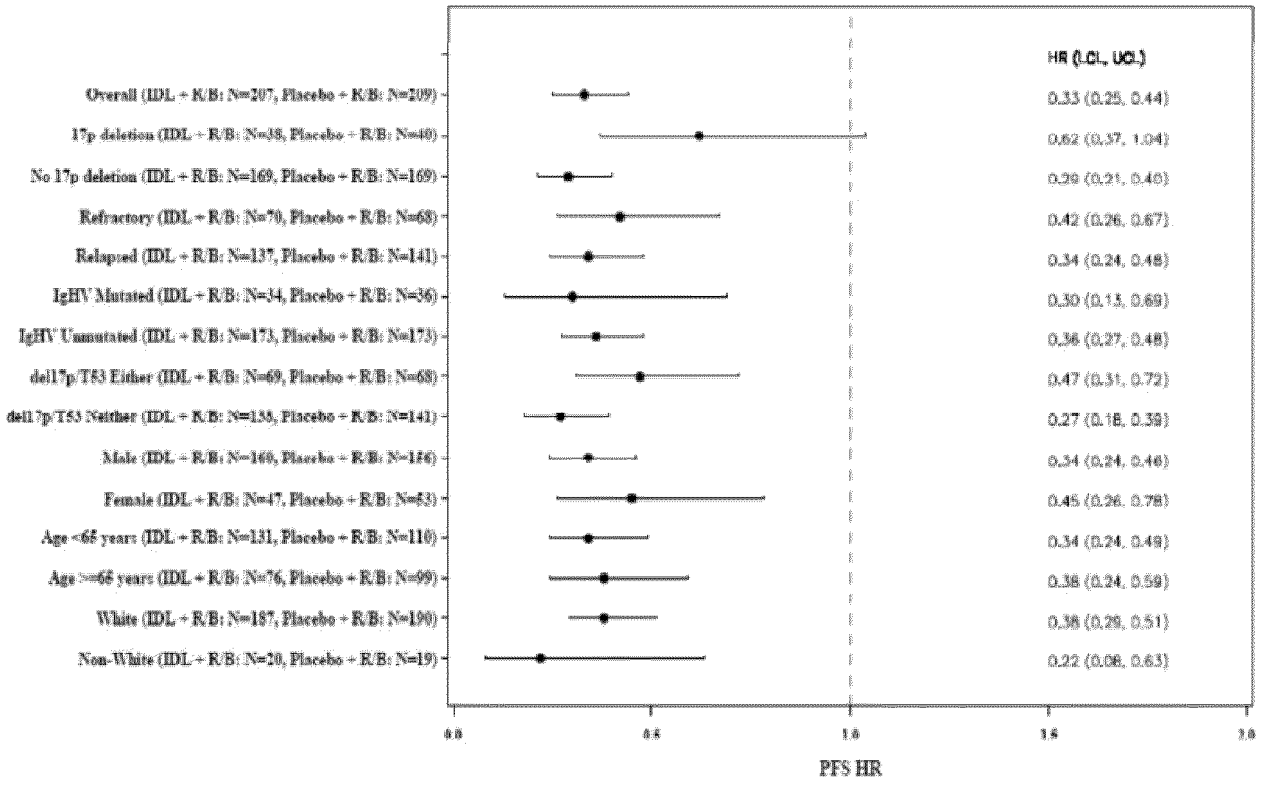
	IDL + BR (N = 207)	PI + BR (N = 209)
Number (%) of Subjects with Events	84 (40.6)	149 (71.3)
Disease Progression	60 (29.0)	130 (62.2)
Death	24 (11.6)	19 (9.1)
Number (%) of Subjects Censored	123 (59.4)	60 (28.7)
Ongoing	82 (39.6)	31 (14.8)
Discontinued Study	39 (18.8)	27 (12.9)
Received Another Antitumor Treatment	2 (1.0)	2 (1.0)
KM Estimate of PFS (Months)[a]		
Q1 (95% CI)	11 (8.3, 13.6)	6.9 (5.6, 8.1)
Median (95% CI)	20.8 (16.6, 26.4)	11.1 (8.9, 11.1)
Q3 (95% CI)	30.3 (26.4, NR)	16.1 (14.0, 19.3)
KM of PFS Rate [95% CI]		
At 24 weeks	88.5 (83.0, 92.3)	82.1 (76.0, 86.7)
At 48 weeks	75.0 (68.0, 80.6)	50.5 (43.2, 57.5)
Adjusted HR (95% CI)[b]	0.33 (0.25, 0.44)	
P-value[c]	6.540×10^{-16}	

BR = bendamustine + rituximab, CI = confidence interval, HR = hazard ratio, IDL = idelalisib, IRC = independent review committee, KM = Kaplan-Meier, NR = not reached, PFS = progression-free survival; PI = placebo, Q1 = first quartile, Q3 = third quartile,
a PFS (months) = (minimum [date of PD, date of death] – date of randomization + 1) / 30.4375.
b HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors in EDC (17p deletion/TP53 mutation, IGHV mutation status, and disease status).
c P-value is from stratified log-rank test, adjusted for randomization stratification factors.

Comment: With event rates of 70% and 40% and the observed differences, the event curves are likely to be stable and the results are considered convincing. Note that BR is administered for 6 four week cycles, while IDL is administered until PD or unacceptable toxicity.

Due to the magnitude of the treatment effect investigator assessed PFS will not be requested.

Forest plot PFS



Comment: There are no conspicuous findings.

Secondary and exploratory endpoints

ORR by IRC Assessment (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)
Best Overall Response, n (%)		
Complete Response (CR)	3 (1.4)	0
Complete Response with Incomplete Marrow Recovery (CRi)	0	1 (0.5)
Partial Response (PR)	142 (68.6)	93 (44.5)
Stable Disease (SD)	47 (22.7)	85 (40.7)
Progressive Disease (PD)	1 (0.5)	19 (9.1)
Not Evaluable (NE)	14 (6.8)	11 (5.3)
ORR[a]	145 (70.0)	94 (45.0)
95% CI[b]	63.3, 76.2	38.1, 52.0
Odds Ratio for Overall Response[c]	3.09	
95% CI for Odds Ratio	2.02, 4.72	
P-value	1.054×10^{-7}	

BR = bendamustine + rituximab, CI = confidence interval, IDL = idelalisib, IRC = Independent Review Committee, ORR = overall response rate, Pl = placebo

a ORR was the percentage of subjects who had best overall response of CR, CRi, or PR.

b 95% CI for ORR was based on the exact method.

c Odds ratio, 95% CI, and p-value were calculated from the CMH Chi-square test stratified by stratification factors in EDC (17p deletion/TP53 mutation, IGHV mutation status, and disease status).

Subjects with CR, CRi, or PR who maintained the response for at least 12 weeks were defined to have confirmed response. Otherwise, response status was categorized as SD.

An additional 22 subjects in the IDL + BR group and 8 subjects in the placebo + BR group potentially could have met the criteria for CR, but did not undergo a bone marrow biopsy.

Time to response: Among subjects who responded, the median (Q1, Q3) TTR was 2.9 (2.8, 3.3) months for both treatment groups (IDL + BR, N = 145; placebo + BR, N = 94).

Lymph Node Response Rate by IRC Assessment (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)
LNR Rate[a]	186/192 (96.9)	120/197 (60.9)
95% CI for LNR Rate[b]	93.3, 98.8	53.7, 67.8
Odds Ratio[c]	28.72	
95% CI for Odds Ratio	10.48, 78.72	
P-value	1.681×10^{-19}	

BR = bendamustine + rituximab, CI = confidence interval, IDL = idelalisib, LNR = lymph node response, Pl = placebo

Analysis only included subjects in the ITT analysis set who had both baseline and at least 1 evaluable postbaseline SPD.

a LNR rate was defined as the percentage of subjects who achieved a $\geq$ 50% decrease from baseline in the SPD of index lymph nodes. (Denominator is the number of subjects with baseline and at least 1 postbaseline measurement.)

b 95% CI for response rate was based on the exact method.

c Odds ratio, 95% CI, and p-value was calculated from the CMH Chi-square test stratified by stratification factors in EDC (17p deletion/TP53 mutation, IGHV mutation status, and disease status).

Splenomegaly and Hepatomegaly Response Rates (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)
Splenomegaly Response Rate[a]	125/148 (84.5%)	80/141 (56.7%)
95% CI[b]	77.6, 89.9	48.1, 65.0
Hepatomegaly Response Rate[c]	57/99 (57.6%)	47/109 (43.1%)
95% CI[b]	47.2, 67.5	33.7, 53.0

BR = bendamustine + rituximab, CI = confidence interval, IDL = idelalisib, Pl = placebo

a Analysis only included subjects who had splenomegaly at baseline and had at least 1 evaluable postbaseline spleen measurement. Responders were subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or to ≤ 12 cm by imaging.

b 95% CI for the response rate was based on the exact method.

c Analysis only included subjects who had hepatomegaly at baseline and had at least 1 evaluable postbaseline liver measurement. Responders were subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging.

ALC, Platelet, Hemoglobin, and ANC Response Rates (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)
ALC Response Rate[a]	169/170 (99.4%)	158/165 (95.8%)
95% CI[b]	96.8, 100	91.5, 98.3
Platelet Response Rate[c]	71/80 (88.8%)	49/63 (77.8%)
95% CI[b]	79.7, 94.7	65.5, 87.3
Hemoglobin Response Rate[d]	58/66 (87.9%)	50/71 (70.4%)
95% CI[b]	77.5, 94.6	58.4, 80.7
ANC Response Rate[e]	24/28 (85.7%)	26/32 (81.3%)
95% CI[b]	67.3, 96.0	63.6, 92.8

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; BR = bendamustine + rituximab, CI = confidence interval, IDL = idelalisib, Pl = placebo,

a Analysis only included subjects who had lymphocytosis (ALC ≥ 4×10^9/L) at baseline and had ALC values 28 days postbaseline. Responders were subjects who achieved on-study ALC < 4×10^9/L or ≥ 50% decrease in ALC from baseline.

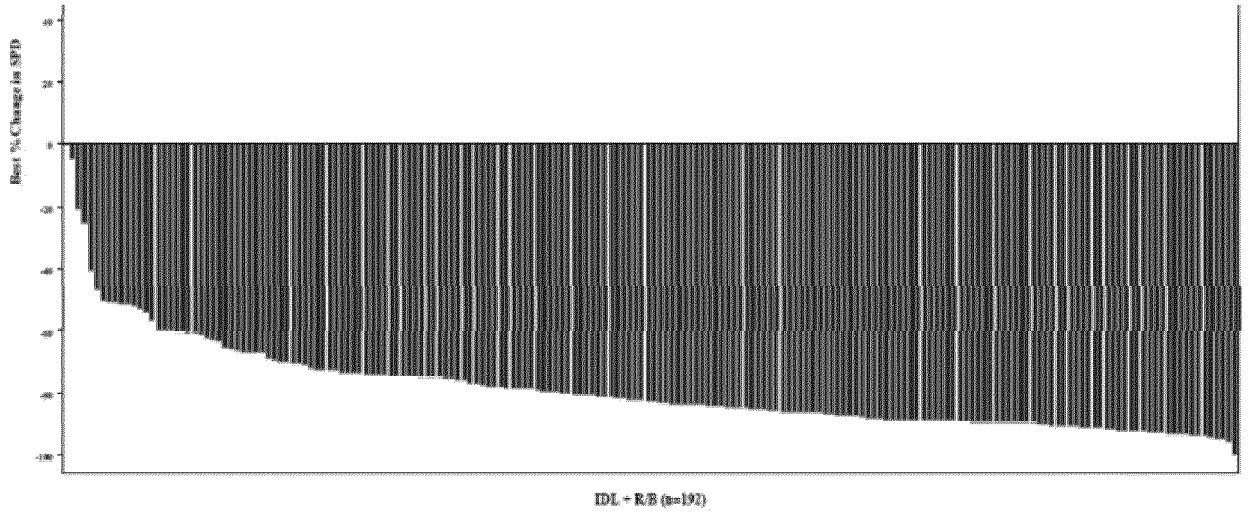
b 95% CI for the response rate was based on the exact method.

c Analysis only included subjects who had thrombocytopenia (platelet count < 100×10^9/L) at baseline and had platelet values 28 days postbaseline. Responders were subjects who achieved on-study platelet count of ≥ 100×10^9/L or ≥ 50% increase in platelet count from baseline.

d Analysis only included subjects who had anemia (hemoglobin < 110 g/L [11 g/dL]) at baseline and had hemoglobin values 28 days postbaseline. Responders were subjects who achieved on-study hemoglobin ≥ 110 g/L (11 g/dL) or ≥ 50% increase in hemoglobin from baseline.

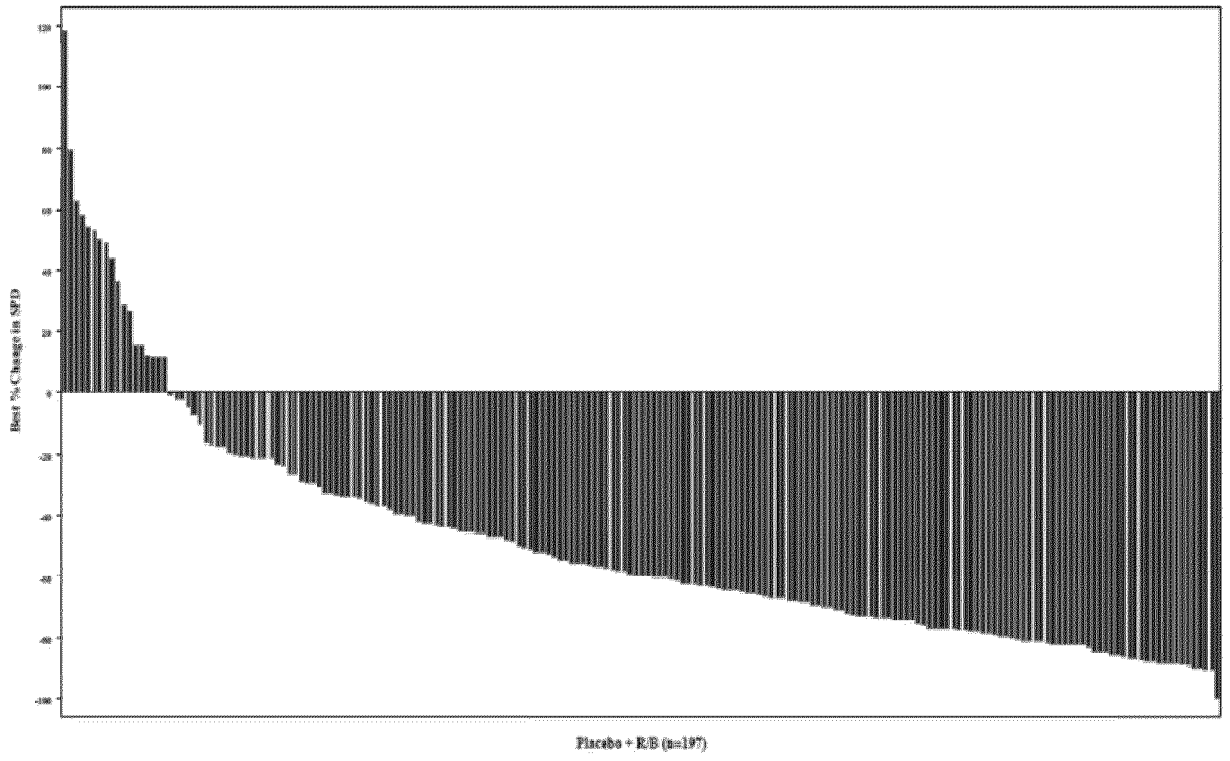
e Analysis only included subjects who had neutropenia (ANC ≤ 1.5×10^9/L) at baseline and had ANC values 28 days postbaseline. Responders were subjects who achieved on-study ANC of > 1.5×10^9/L or ≥ 50% increase in ANC from baseline.

Waterfall Plot of Best Percent Change from Baseline in SPD per IRC Assessment: IDL + BR Group (ITT)



B = bendamustine, IDL = idelalisib, IRC = independent review committee, R = rituximab, SPD = sum of the products of greatest perpendicular diameters

Waterfall Plot of Best Percent Change from Baseline in SPD per IRC Assessment: Placebo + BR Group (ITT)



Comment: Irrespective of response parameter, IDL shows a major add-on effect to BR. The only exception of interest is CR, but note that the frequency might be underestimated due to missing bone marrow data (22 vs. 8 individuals).

MRD is not mentioned in the protocol or the study report .

Note absence of progression as best response in the IDL+BR arm.

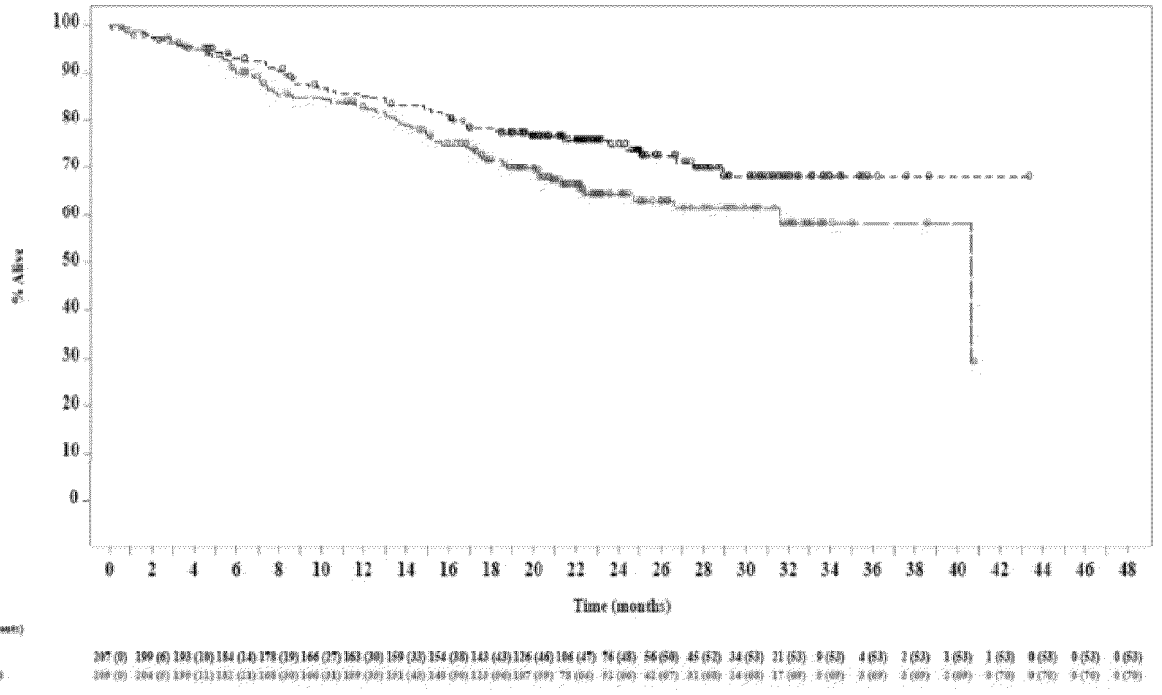
Overall Survival based on Data through 02 May 2016 (ITT)

	IDL + BR (N = 207)	Pl + BR (N = 209)
Number (%) of Subjects with Events	53 (25.6)	70 (33.5)
Death	53 (25.6)	70 (33.5)
Number (%) of Subjects Censored	154 (74.4)	139 (66.5)
Discontinued Study	84 (40.6)	116 (55.5)
Ongoing	70 (33.8)	23 (11.0)
KM Estimate of OS (Months)[a]		
Q1 (95% CI)	23.5 (16, NR)	15.7 (13.2, 20.3)
Median (95% CI)	NR (NR, NR)	40.6 (31.6, NR)
Q3 (95% CI)	NR (NR, NR)	NR (40.6, NR)
Adjusted HR (95% CI)[b]	0.67 (0.47, 0.96)	
P-value from Stratified Log-Rank Test	3.637×10^{-2}	
P-value from Unstratified Log-Rank Test	5.874×10^{-2}	

BR = bendamustine + rituximab, CI = confidence interval, HR = hazard ratio, IDL = idelalisib, KM = Kaplan Meier, NR = not reached, Pl = placebo, OS = overall survival, Q1 = first quartile, Q3 = third quartile

a OS (months) = (date of death – date of randomization + 1) / 30.4375

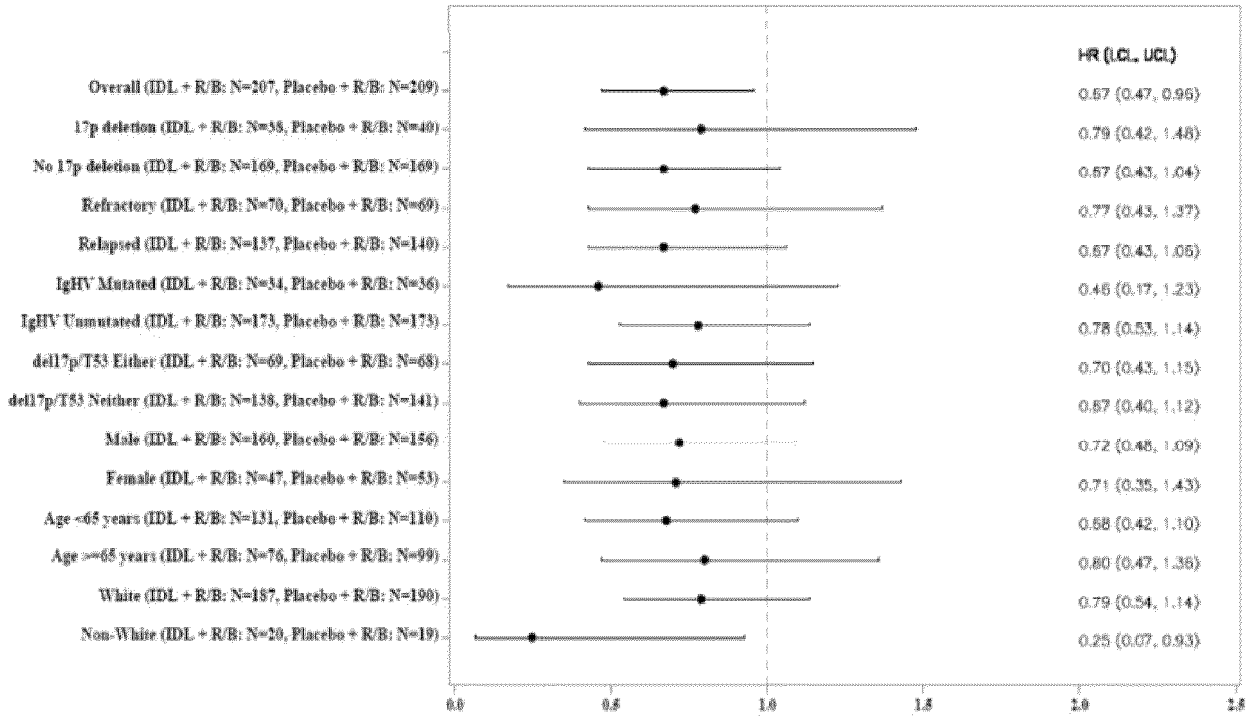
b Hazard ratio and 95% CI were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation status, and disease status).



Comment: Note that 40 and 55% has discontinmued the study and were censored in the OS analysis. After discontinuation, follow-up for survival was undertaken every 6 months. It is unclear if all patients accepted to participate in the long term OS follow-up and if missingness is an issue, reasons for censoring is thus unknown I patients who left the study.

Data are considered immature.

Forest Plot for Overall Survival based on Data through 02 May 2016 (ITT)



Ancillary analyses

Efficacy Analysis by 17 p deletion and/or TP53 Mutation Status

This study included 137 subjects with 17p deletion and/or TP53 mutation (69 in the IDL + BR group and 68 Pl + BR), and 279 subjects with neither 17p deletion nor TP53 mutation (138 IDL + BR and 141 Pl + BR group). Efficacy results for both groups are summarized in the table below.

Efficacy Results by 17p Deletion and/or TP53 Mutation Status (ITT Analysis Set, Study GS-US-312-0115)

Endpoint (Measure)	Subjects with 17p Deletion and/or TP53 Mutation		Subjects with Neither 17p Deletion nor TP53 Mutation	
	IDL+BR (N = 69)	PI+BR (N = 68)	IDL+BR (N = 138)	PI+BR (N = 141)
KM estimate of PFS, median (95% CI) months[a] (data through 07 Oct 2015)	11.3 (8.8, 16.6)	8.3 (5.9, 8.5)	24.6 (19.5, 30.3)	11.2 (11.1, 13.6)
PFS, unadjusted HR (95% CI)[b] (data through 07 Oct 2015)	0.47 (0.31, 0.72)		0.27 (0.18, 0.39)	
Odds ratio for Overall Response (95% CI)[c] (data through 07 Oct 2015)	4.67 (2.25, 9.70)		2.45 (1.47, 4.06)	
Odds ratio for LNR (95% CI)[c] (data through 07 Oct 2015)	31.29 (9.91, 98.82)		22.81 (5.36, 97.01)	
OS, Unadjusted HR (95% CI)[d] (data through 07 Oct 2015)	0.61 (0.36, 1.03)		0.65 (0.36, 1.18)	
OS, Unadjusted HR (95% CI)[d] (data through 02 May 2016)	0.7 (0.43, 1.15)		0.67 (0.4, 1.12)	
KM estimate of DOR, median (95% CI) months[e, f, g] (data through 07 Oct 2015)	11.1 (10.8, NR)	10.5 (5.6, 13.7)	22.8 (20.0, 27.2)	11.2 (8.6, 16.6)

BR = bendamustine + rituximab; DOR = duration of response; HR = hazard ratio; IDL = idelalisib; KM = Kaplan-Meier; LNR = lymph node response rate; NR = not reached; OS = overall survival; PFS = progression free survival

a PFS (months) = (minimum [date of PD, date of death] – date of randomization + 1) / 30.4375.

b HR and 95% CIs are calculated using the Cox proportional hazards model without any adjustment.

c Odds ratio and 95% CI were calculated without any adjustment.

d HR and 95% CI were calculated using the Cox proportional hazards model without any adjustments.

e DOR (months) = (minimum [date of PD, date of death] – date of first documented CR, CRi, or PR + 1) / 30.4375

f Analysis included only subjects who achieved a CR, CRi, or PR.

g Subjects with CR, CRi, or PR who maintained the response for at least 12 weeks were defined to have confirmed response. Otherwise, response status was categorized as SD.

Efficacy analysis by only 17p deletion status Efficacy results for subjects with 17p deletion (n=38 IDL + BR and n=40 Pl + BR) or without (n=169 IDL + BR and n=169 Pl + BR) are summarized in the following table: Efficacy Results by only 17p Deletion Status (Study GS-US-312-0115)

Endpoint (Measure)	Subjects with 17p Deletion		Subjects without 17p Deletion	
	IDL+BR (N = 38)	Pl+BR (N = 40)	IDL+BR (N = 169)	Pl+BR (N = 169)
KM estimate of PFS, median (95% CI) months[a] (data through 07 Oct 2015)	11.0 (7.9, 13.3)	5.9 (3.4, 8.4)	24.6 (19.5, 30.3)	11.1 (10.8, 11.5)
PFS, unadjusted HR (95% CI)[b] (data through 07 Oct 2015)	0.62 (0.37, 1.04)		0.29 (0.21, 0.40)	
Odds ratio for Overall Response (95% CI)[c] (data through 07 Oct 2015)	4.74 (1.77, 12.65)		2.64 (1.68, 4.16)	
Odds ratio for LNR (95% CI)[c] (data through 07 Oct 2015)	42.67 (8.44, 215.82)		18.38 (6.46, 52.28)	
OS, Unadjusted HR (95% CI)[d] (data through 07 Oct 2015)	0.72 (0.36, 1.42)		0.65 (0.40, 1.06)	
OS, Unadjusted HR (95% CI)[d] (data through 02 May 2016)	0.79 (0.42, 1.48)		0.67 (0.43, 1.04)	
KM estimate of DOR, median (95% CI) months[e, f, g] (data through 07 Oct 2015)	11.1 (8.0, 23.7)	13.6 (5.4, 15.7)	22.8 (20.0, NR)	11.2 (8.4, 16.2)

BR = bendamustine + rituximab; DOR = duration of response; HR = hazard ratio; IDL = idelalisib; KM = Kaplan-Meier; LNR = lymph node response rate; NR = not reached; OS = overall survival; PFS = progression free survival

a PFS (months) = (minimum [date of PD, date of death] – date of randomization + 1) / 30.4375.
b HR and 95% CIs are calculated using the Cox proportional hazards model without any adjustment.
c Odds ratio and 95% CI were calculated without any adjustment.
d HR and 95% CI were calculated using the Cox proportional hazards model without any adjustments.
e DOR (months) = (minimum [date of PD, date of death] – date of first documented CR, CRi, or PR + 1) / 30.4375
f Analysis included only subjects who achieved a CR, CRi, or PR.
g Subjects with CR, CRi, or PR who maintained the response for at least 12 weeks were defined to have confirmed response. Otherwise, response status was categorized as SD.

Comments

The improvement in PFS with IDL + BR was lower for patients with 17p deletion and/or TP53 mutation (3 months) and patients with 17p deletion (5.1 months), compared to the overall study population (9.7 months). KM curves for 17p deletion patients have been provided, but should also be presented for patients with or without 17p deletion and/or TP53 mutation. Furthermore, the applicant is asked to discuss the observed differences in PFS improvement between these two patient groups.

The ORR was 60.9% with IDL + BR vs. 25% with placebo + BR in patients with 17p deletion and/or TP53 mutation. In patients with 17p deletion, the ORR was 57.9% vs 22.5%, respectively.

No significant differences in OS have been observed for both patient groups.

HRQOL

EQ-5D, KPS, FACT-Leu: No specific hypotheses were tested and there was no alpha protection. No differences between treatment arms were demonstrated.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application and should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Study GS-US-312-0115

Population: CLL previously treated with purine analogue and anti-CD20 MoAb, with progressive disease warranting therapy (IWCLL)

Study period: 15 June 2012 (First Subject Screened)

02 May 2016 (Assessments of Safety and Overall Survival). The study is ongoing.

Design: Double blind: Bendamustine + rituximab +IDL/Placebo in labelled dosages

Randomisation: 1:1, fixed-block centralized randomization

Stratification: 17p deletion and/or TP53 mutation in CLL cells

Immunoglobulin heavy chain variable region (IGHV) mutation

Disease status: refractory versus relapsed

Outcome measures:

Primary PFS by IRC

Secondary Overall response rate (ORR), lymph node response (LNR) rate, and complete response (CR) rate (type 1 control).

Additional OS (formally no control of alpha), HRQoL, etc.

PFS	**IDL + BR (N = 207)**	**PI + BR (N = 209)**
Number (%) of Subjects with Events	84 (40.6)	149 (71.3)
Disease Progression	60 (29.0)	130 (62.2)
Death	24 (11.6)	19 (9.1)
KM Estimate of PFS (Months)[a]		
Median (95% CI)	20.8 (16.6, 26.4)	11.1 (8.9, 11.1)
At 24 weeks	88.5 (83.0, 92.3)	82.1 (76.0, 86.7)
At 48 weeks	75.0 (68.0, 80.6)	50.5 (43.2, 57.5)
Adjusted HR (95% CI)[b]	0.33 (0.25, 0.44)	
P-value[c]	6.540×10^{-16}	

OS (02 May 2016)	**IDL + BR (N = 207)**	**PI + BR (N = 209)**
Number (%) of Subjects with Events	53 (25.6)	70 (33.5)
KM Estimate of OS (Months)[a]		
Q1 (95% CI)	23.5 (16, NR)	15.7 (13.2, 20.3)
Median (95% CI)	NR (NR, NR)	40.6 (31.6, NR)
Adjusted HR (95% CI)[b]	0.67 (0.47, 0.96)	
P-value from Stratified Log-Rank Test	0.0364	

Response Rate	**IDL + BR (N = 207)**	**PI + BR (N = 209)**

Best Overall Response, n (%)[a]		
Complete Response (CR)	3 (1.4)	0
Partial Response (PR)	142 (68.6)	93 (44.5)
Progressive Disease (PD)	1 (0.5)	19 (9.1)
ORR (CR+CRi+PR)	145 (70.0)	94 (45.0)
95% CI[c]	63.3, 76.2	38.1, 52.0

Analysis performed across trials

Enrolment Criteria for Studies GS-US-312-0115, GS-US-312-0119, GS-US-312-0116

Study GS-US-312-0115	**Study GS-US-312-0119**	**Study GS-US-312-0116**
Relapsed CLL with prior treatment with the following: • ≥ 2 cycles of a regimen containing a purine analog (eg, fludarabine, pentostatin, cladribine) or bendamustine, and • ≥ 2 doses with a regimen containing an anti-CD20 monoclonal antibody (eg, rituximab, ofatumumab, obinutuzumab)	Relapsed CLL with prior treatment comprising therapy with either of the following given alone or in combination: • A purine analog (eg, fludarabine, pentostatin, cladribine) administered for ≥ 2 cycles of cytotoxic treatment or • Bendamustine administered for ≥ 2 cycles of treatment	Relapsed CLL with prior treatment with any of the following: • ≥ 1 regimen containing a therapeutic anti-CD20 monoclonal antibody administered for ≥ 2 doses of antibody treatment • ≥ 1 cytotoxic agent administered for ≥ 2 cycles of cytotoxic treatment
Sufficiently fit to receive cytotoxic chemotherapy, including ANC ≥ 1.5 x 10^9/L, platelets ≥ 75 x 10^9/L, and hemoglobin ≥ 100 g/L (10.0 g/dL or 6.2 mmol/L) (although ≥ Grade 2 neutropenia, thrombocytopenia, or anemia was permitted if abnormality was related to bone marrow involvement with CLL [as documented by bone marrow biopsy/aspirate obtained since the last prior therapy] Creatinine clearance ≥ 40 mL/min No restrictions regarding CIRS score	No restrictions regarding myelotoxicity; creatinine clearance > 30 ml/min; any CIRS score	Unfit to receive cytotoxic therapy because of chemotherapy-induced myelotoxicity or creatinine clearance > 30 and < 60 mL/min or comorbidities as measured by CIRS score > 6
Karnofsky performance score of ≥ 60	Karnofsky performance score of ≥ 60	Karnofsky performance score of ≥ 40

CIRS = cumulative illness rating scale; ANC = absolute neutrophil count

OS for Individual Phase 3 Studies (ITT Analysis Sets)

	Study GS-US-312-0115 (Data through 02 May 2016)		Study GS-US-312-0119		Study GS-US-312-0117 (by Initial Randomization in Study GS-US-312-0116)	
	IDL + BR N = 207	PI + BR N = 209	IDL + O N = 174	O Alone N = 87	IDL + R N = 110	PI + R N = 110
Number (%) of Subjects Who Died	53 (25.6)	70 (33.5)	63 (36.2)	32 (36.8)	38 (34.5)	49 (44.5)
Number (%) of Subjects Censored	53 (25.6)	70 (33.5)	111 (63.8)	55 (63.2)	72 (65.5)	61 (55.5)
Ongoing	154 (74.4)	139 (66.5)	34 (19.5)	1 (1.1)	10 (9.1)	13 (11.8)
Discontinued Study	84 (40.6)	116 (55.5)	77 (44.3)	54 (62.1)	62 (56.4)	48 (43.6)
KM Estimate of OS (Months)[a]						
Q1 (95% CI)	23.5 (16, NR)	15.7 (13.2, 20.3)	18.2 (12.3, 22.9)	12.7 (6.0, 19.3)	20.5 (15.4, 25.4)	9.2 (7.3, 12.6)
Median (95% CI)	NR (NR, NR)	40.6 (31.6, NR)	NR (31.5, NR)	30.2 (23.0, NR)	NR (28.5, NR)	37.3 (16.6, NR)
Q3 (95% CI)	NR (NR, NR)	NR (40.6, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Adjusted Hazard Ratio (95% CI)	0.67 (0.47, 0.96)[b]		0.74 (0.48, 1.14)[b]		0.63 (0.41, 0.96)[c]	
P-value From Stratified Log-Rank Test	0.0364[d]		0.1995[d]		0.0029[e]	

PFS for Individual Phase 3 Studies (ITT)

	Study GS-US-312-0115		Study GS-US-312-0119		Study GS-US-312-0116	
	IDL + BR N = 207	PI + BR N = 209	IDL + O N = 174	O Alone N = 87	IDL + R N = 110	PI + R N = 110
Number (%) of Subjects with Events	84 (40.6)	149 (71.3)	103 (59.2)	57 (65.5)	25 (22.7)	70 (63.6)
Disease Progression	60 (29.0)	130 (62.2)	76 (43.7)	51 (58.6)	17 (15.5)	62 (56.4)
Death	24 (11.6)	19 (9.1)	27 (15.5)	6 (6.9)	8 (7.3)	8 (7.3)
Number (%) of Subjects Censored	123 (59.4)	60 (28.7)	71 (40.8)	30 (34.5)	85 (77.3)	40 (36.4)
Completed Study/Crossed over to Open-Label IDL	NA	NA	NA	NA	69 (62.7)	33 (30.0)
Ongoing	82 (39.6)	31 (14.8)	28 (16.1)	1 (1.1)	–	–
Discontinued Study	39 (18.8)	27 (12.9)	37 (21.3)	28 (32.2)	16 (14.5)	7 (6.4)
Received Another Antitumor Treatment	2 (1.0)	2 (1.0)	0	1 (1.1)	0	0
Missed ≥ 2 Consecutive Tumor Measurements	0	0	6 (3.4)	0	0	0
KM Estimate of PFS (Months)[c]						
Q1 (95% CI)	11 (8.3, 13.6)	6.9 (5.6, 8.1)	8.6 (7.5, 10.8)	3.5 (1.8, 5.3)	10.7 (8.3, 13.9)	3.5 (1.8, 3.8)
Median (95% CI)	20.8 (16.6, 26.4)	11.1 (8.9, 11.1)	16.6 (13.6, 21.7)	8.0 (5.7, 8.2)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
Q3 (95% CI)	30.3 (26.4, NR)	16.1 (14.0, 19.3)	31.1 (24.9, NR)	9.2 (8.2, 16.4)	NR (19.4, NR)	8.3 (8.1, 10.9)
Adjusted Hazard Ratio (95% CI)	0.33 (0.25, 0.44)[f]		0.24 (0.17, 0.35)[f]		0.15 (0.09, 0.24)[d]	
P-value from Stratified Log-Rank Test	< 0.0001[g]		< 0.0001[g]		< 0.0001[g]	

2.3.3.6. Discussion on clinical efficacy (Rapporteur)

Study 312-0115 is a standard, well-conducted add-on study of IDL vs. placebo on a background of bendamustine+ rituximab in patients previously treated with a purine analogue and an anti-CD20 MoAb.

In patients likely to tolerate bendamustine + rituximab, e.g. based on tolerability to prior lines of therapy, this is an appropriate design, also in del17p/*TP53* CLL when the study was initiated. Patients were pre-treated with a median of two prior regimens, about 1/3 were characterised as refractory and

similarly 1/3 showed del.17p/*TP53*. There were no imbalances of likely importance. Information as regards the last prior regimen is requested **(OC)**. If bendamustine was part of the last regimen, ORR and PFS on study therapies should be reported.

In terms of standard outcome measures, superiority in terms of ORR and PFS has been convincingly demonstrated. It should be noticed that BR was administered for six cycles followed by IDL or placebo only. It is therefore of importance that a survival benefit has been shown, even though only borderline (p=0.036). Survival data are immature at an event rate of about 30%, however, and the event rate per time period is low, i.e. it is less likely that a meaningful increase is reachable within this procedure. Clarification should be provided as regards sampling of survival data after study discontinuation, especially missingness. Time to next-line therapy and selected next-line regimens should be submitted.

The conducted subgroup analyses raise no concerns, but the submitted forest plots should be resubmitted with medians added.

2.3.3.7. Conclusions on the clinical efficacy

Superior efficacy in terms of ORR and PFS has been convincingly demonstrated. Due to the design (and toxicity) survival data are considered essential.

2.3.3.8. Discussion on clinical efficacy (CoRapporteur)

The positive efficacy results of pivotal study GS-US-312-015 suggest a clinically relevant improvement in PFS, OS and ORR for the IDL +BR combination compared to placebo + BR. However, the precise target population of the triple combination is unclear in the context of the already approved idelalisib indication for relapsed and refractory CLL patients that encompasses the current study population. This is in particular relevant considering the adverse safety profile of the triple combination relative to the PFS results in the 0115 study population vs those in the non-fit population treated with IDL + R. This will be further discussed in the B/R section of this report, but, for reference, in the IDL + R study GS-US-312-0116, median PFS was 19.4 months in the IDL + R arm, compared to 6.5 months for placebo + R, which indicates an improvement in median PFS of 12.9 month due to the addition of IDL. A lower improvement in median PFS was observed for the addition of IDL to the BR backbone in pivotal study GS-US-312-0115. For the secondary endpoints ORR, and OS, as well as HRQoL the results showed the same pattern. Importantly, for the IDL + R regime, the treatment effect was equally profound in the adverse genetics subgroups of 17p deletion and/or TP53 mutation, while the clinical benefit in terms of PFS in this patient group seems to be lower with IDL + BR.

The study population of the current pivotal trial with IDL + BR (eligible for chemotherapy) differed from the study population for the IDL + R study 0116 (non-eligible for chemotherapy). Acknowledging the uncertainties associated with cross-study comparison, for the more fit IDL + BR study population with less comorbidities and less advanced disease, improved efficacy results would have been expected compared to results for the non-fit IDL + R study population. The clinical benefit of the addition of bendamustine to the approved IDL + R combination is thus uncertain in relation to the applied for indication and the question is whether patients eligible for chemotherapy would not also benefit from IDL + R alone.

2.3.3.9. Conclusions on clinical efficacy

Altogether, in pivotal study GS-US-312-015 statistically significant increases in PFS, OS, and ORR were observed for the combination of IDL with BR compared to placebo + BR. However, the clinical benefit of the addition of bendamustine to the approved IDL + R combination is uncertain in the applied for

indication. The applicant should discuss the precise target population of the triple combination, in the context of the results observed for relapsed/refractory CLL for the already approved idelalisib indication.

2.3.3.10. Clinical safety

Introduction

Serious infections, including opportunistic infections, constitute the main concern in the treatment with IDL, especially in combination with other immune-suppressive agents such as bendamustine and anti-CD20 MoAbs. Late colitis in need of steroid therapy, such as budesonide, is a specific IDL reaction. Severe skin toxicity is also seen especially when combined with other drugs known to elicit this type of toxicity (SJS and TEN)

Study Drug Exposure (Safety Analysis Set)

	IDL + BR (N = 207)	Pl + BR (N = 209)	Total (N = 416)
Duration of Exposure to IDL/Pl (Months)[a]			
N	207	208	415
Mean (StD)	16.1 (10.25)	11.4 (6.49)	13.7 (8.88)
Median	18.2	11.1	13.4
Q1, Q3	5.8, 24.0	5.8, 16.6	5.8, 20.3
Min, Max	0, 43.4	0.5, 28.5	0, 43.4
Cumulative Exposure to IDL/Pl, n (%)			
≥ 1 Day	207 (100.0)	208 (99.5)	415 (99.8)
≥ 2 months	186 (89.9)	199 (95.2)	385 (92.5)
≥ 4 months	171 (82.6)	173 (82.8)	344 (82.7)
≥ 6 months	154 (74.4)	154 (73.7)	308 (74.0)
≥ 12 months	127 (61.4)	90 (43.1)	217 (52.2)
≥ 18 months	104 (50.2)	34 (16.3)	138 (33.2)
≥ 24 months	51 (24.6)	9 (4.3)	60 (14.4)
≥ 30 months	17 (8.2)	0	17 (4.1)
≥ 36 months	2 (1.0)	0	2 (0.5)
Subjects with No Dose Modification, n (%)	88 (42.5)	154 (73.7)	–
Subjects with Dose Modification, n (%)	119 (57.5)	55 (26.3)	–
Subjects with Dose Interruption	117 (56.5)	54 (25.8)	–
Subjects with Dose Rechallenged[b]	117 (54.5)	54 (25.8)	–
Subjects Rechallenged at 150 mg	87 (42.0)	40 (19.1)	–
Subjects Rechallenged at 100 mg	30 (14.5)	14 (6.7)	–
Subjects With Dose Re-escalation	11 (5.3)	4 (1.9)	–
Subjects with Dose Reduction Without Interruption	2 (1.0)	1 (0.5)	–
Subjects with Dose Re-escalated	1 (0.5)	0	–
Modification due to AE	101 (48.8)	46 (22.0)	–
Modification due to Other	1 (0.5)	2 (1.0)	–
Modification due to AE and Other	17 (8.2)	7 (3.3)	–

AE = adverse event, BR = bendamustine + rituximab, IDL = idelalisib, Pl = placebo, Q1 = first quartile, Q3 = third quartile, StD = standard deviation.

a Duration of exposure (months) = (min [last IDL/Pl dosing date as captured on study drug completion eCRF page, data cutoff date] - first IDL/Pl dosing date + 1) / 30.4375.

b First rechallenged dose after the first interruption was considered for this analysis.

Subject [redacted] in the IDL + BR group was dispensed 1 bottle of placebo; this was reported as an important protocol deviation (Appendix 16.2, Listing 4.4).

Comment: Note that BR was to be administered for 6 cycles (á 4 weeks) followed by placebo or IDL.

Overall Summary of Adverse Events (Safety Analysis Set)

Adverse Event Category, n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)
Any AE	207 (100)	203 (97.1)
IDL/Pl-Related AE	170 (82.1)	125 (59.8)
Rituximab-Related AE	145 (70.0)	145 (69.4)
Bendamustine-Related AE	168 (81.2)	173 (82.8)
≥ Grade 3 AE	196 (94.7)	163 (78.0)
≥ Grade 3 IDL/Pl-Related AE	141 (68.1)	68 (32.5)
≥ Grade 3 Rituximab-Related AE	105 (50.7)	83 (39.7)
≥ Grade 3 Bendamustine-Related AE	148 (71.5)	120 (57.4)
Any SAE	147 (71.0)	94 (45.0)
IDL/Pl-Related SAE	75 (36.2)	28 (13.4)
Rituximab-Related SAE	48 (23.2)	28 (13.4)
Bendamustine-Related SAE	70 (33.8)	40 (19.1)
AE Leading to IDL/Pl Dose Reduction	34 (16.4)	13 (6.2)
AE Leading to IDL/Pl Dose Interruption	122 (58.9)	49 (23.4)
AE Leading to IDL/Pl Discontinuation	68 (32.9)	31 (14.8)
AE Leading to Death	25 (12.1)	19 (9.1)

BR = bendamustine + rituximab, IDL = idelalisib, NA = not applicable, Pl = placebo
Relationship to study drug was determined by investigator; AEs with missing relationships were considered to be related.

Comment:"Relatedness" was determined by the investigators. With respect to"any AE" it is of interest to notice the similarity between treatment arms for bendamustin and rituximab related AEs and the clear difference with respect to SAE and grade ≥3, a reasonable interpretation being that IDL adds to BR "related" AE. Overall IDL adds considerably to the toxicity of BR.

Adverse Events Reported for ≥ 10% of Subjects in Either Treatment Group by Decreasing SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term, n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)
Number of Subjects with AEs	207 (100.0)	203 (97.1)
Blood and Lymphatic System Disorders	160 (77.3)	146 (69.9)
Neutropenia	132 (63.8)	114 (54.5)
Anaemia	55 (26.6)	50 (23.9)
Febrile Neutropenia	49 (23.7)	13 (6.2)
Thrombocytopenia	43 (20.8)	46 (22.0)
Infections and Infestations	150 (72.5)	125 (59.8)
Pneumonia	50 (24.2)	27 (12.9)
Upper Respiratory Tract Infection	36 (17.4)	24 (11.5)
Gastrointestinal Disorders	138 (66.7)	127 (60.8)
Diarrhoea	84 (40.6)	47 (22.5)
Nausea	57 (27.5)	73 (34.9)
Vomiting	34 (16.4)	31 (14.8)
Constipation	32 (15.5)	35 (16.7)
General Disorders and Administration Site Conditions	132 (63.8)	118 (56.5)
Pyrexia	90 (43.5)	63 (30.1)
Fatigue	43 (20.8)	52 (24.9)
Chills	23 (11.1)	13 (6.2)
Asthenia	22 (10.6)	21 (10.0)
Respiratory, Thoracic and Mediastinal Disorders	97 (46.9)	92 (44.0)
Cough	49 (23.7)	48 (23.0)
Dyspnoea	22 (10.6)	28 (13.4)
Skin and Subcutaneous Tissue Disorders	103 (49.8)	81 (38.8)
Rash	35 (16.9)	28 (13.4)
Investigations	90 (43.5)	46 (22.0)
Alanine Aminotransferase Increased	32 (15.5)	3 (1.4)
Weight Decreased	21 (10.1)	12 (5.7)
Metabolism and Nutrition Disorders	74 (35.7)	46 (22.0)
Decreased Appetite	22 (10.6)	15 (7.2)
Musculoskeletal and Connective Tissue Disorders	65 (31.4)	55 (26.3)
Arthralgia	25 (12.1)	16 (7.7)
Nervous System Disorders	56 (27.1)	54 (25.8)
Headache	20 (9.7)	22 (10.5)
Injury, Poisoning and Procedural Complications	43 (20.8)	59 (28.2)
Infusion Related Reaction	31 (15.0)	49 (23.4)

Comment: Note the major increase in infectious events including febrile neutropenia.

≥ Grade 3 AEs Reported for ≥ 2% of Subjects in Either Treatment Group by Decreasing SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term, n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)
Number of Subjects with ≥ Grade 3 AE	196 (94.7)	163 (78.0)
Blood And Lymphatic System Disorders	149 (72.0)	129 (61.7)
Neutropenia	124 (59.9)	99 (47.4)
Febrile Neutropenia	49 (23.7)	13 (6.2)
Anaemia	32 (15.5)	27 (12.9)
Thrombocytopenia	27 (13.0)	26 (12.4)
Leukopenia	12 (5.8)	9 (4.3)
Granulocytopenia	6 (2.9)	6 (2.9)
Autoimmune Haemolytic Anaemia	0	5 (2.4)
Infections and Infestations	85 (41.1)	54 (25.8)
Pneumonia	29 (14.0)	17 (8.1)
Sepsis	12 (5.8)	6 (2.9)
Urinary Tract Infection	5 (2.4)	4 (1.9)
Lower Respiratory Tract Infection	4 (1.9)	6 (2.9)
Neutropenic Sepsis	3 (1.4)	6 (2.9)
Respiratory Tract Infection	3 (1.4)	5 (2.4)
Septic Shock	5 (2.4)	1 (0.5)

Investigations	54 (26.1)	9 (4.3)
Alanine Aminotransferase Increased	22 (10.6)	1 (0.5)
Aspartate Aminotransferase Increased	11 (5.3)	0
Transaminases Increased	8 (3.9)	0
Neutrophil Count Decreased	6 (2.9)	1 (0.5)
Platelet Count Decreased	6 (2.9)	1 (0.5)
Gastrointestinal Disorders	38 (18.4)	13 (6.2)
Diarrhoea	25 (12.1)	4 (1.9)
Abdominal Pain	5 (2.4)	1 (0.5)
General Disorders and Administration Site Conditions	25 (12.1)	23 (11.0)
Pyrexia	15 (7.2)	7 (3.3)
Fatigue	7 (3.4)	5 (2.4)
Asthenia	1 (0.5)	6 (2.9)
Respiratory, Thoracic and Mediastinal Disorders	22 (10.6)	18 (8.6)
Dyspnoea	6 (2.9)	8 (3.8)
Pulmonary Embolism	3 (1.4)	6 (2.9)
Metabolism and Nutrition Disorders	23 (11.1)	14 (6.7)
Hypokalaemia	5 (2.4)	6 (2.9)
Decreased Appetite	5 (2.4)	0
Skin And Subcutaneous Tissue Disorders	18 (8.7)	1 (0.5)
Rash	6 (2.9)	0
Injury, Poisoning and Procedural Complications	9 (4.3)	7 (3.3)
Infusion Related Reaction	5 (2.4)	4 (1.9)

Comment: The apparent discrepancy between the rather minor increase in grade ≥3 neutropenia and the major increase in neutropenic fever and other infections is worth noting.

Incidence of infectious events by Time Interval (Safety Analysis Set)

Adverse Event, n (%)	0 to 12 Weeks		>12 to 24 Weeks		> 24 to 36 Weeks		> 36 to 48 Weeks		> 48 to 60 Weeks	
	IDL + BR (N=207)	Pl + BR (N=209)	IDL + BR (N=207)	Pl + BR (N=209)	IDL + BR (N=207)	Pl + BR (N=209)	IDL + BR (N=207)	Pl + BR (N=209)	IDL + BR (N=207)	Pl + BR (N=209)
Infection										
All Grades	90/207 (43.5)	63/209 (30.1)	78/192 (40.6)	61/200 (30.5)	49/172 (28.5)	45/170 (26.5)	31/144 (21.5)	29/143 (20.3)	22/134 (16.4)	19/109 (17.4)
≥ Grade 3	49/207 (23.7)	29/209 (13.9)	41/192 (21.4)	20/200 (10.0)	21/172 (12.2)	11/170 (6.5)	11/144 (7.6)	6/143 (4.2)	10/134 (7.5)	7/109 (6.4)
Febrile Neutropenia										
All Grades	28/207 (13.5)	8/209 (3.8)	15/192 (7.8)	5/200 (2.5)	3/172 (1.7)	2/170 (1.2)	5/144 (3.5)	0	2/134 (1.5)	0
≥ Grade 3	28/207 (13.5)	8/209 (3.8)	15/192 (7.8)	5/200 (2.5)	3/172 (1.7)	2/170 (1.2)	5/144 (3.5)	0	2/134 (1.5)	0
CMV										
All Grades	4/207 (1.9)	2/209 (1.0)	5/192 (2.6)	0	3/172 (1.7)	0	0	1/143 (0.7)	1/134 (0.7)	0
≥ Grade 3	2/207 (1.0)	2/209 (1.0)	4/192 (2.1)	0	1/172 (0.6)	0	0	1/143 (0.7)	0	0
PJP										
All Grades	0	0	1/192 (0.5)	0	2/172 (1.2)	0	0	0	0	0
≥ Grade 3	0	0	1/192 (0.5)	0	1/172 (0.6)	0	0	0	0	0

Comment: As any grade include less relevant events such as common cold, etc. the focus is on grade ≥3.
Up to week 24, the increase in grade ≥3 infections and febrile neutropenia look as expected. The rather high incidence also after week 24 in the true placebo arm might look surprising but could relate to the prolonged immunosuppresive effects of bendamustine/rituximab and the underlying disease.

Rather few indivuduals had CMV/PJP infections. It is uclear how investigators adhered to recommendations as regards prophylaxis.

Diarrhoea/Colitis

Through the cut-off date (02 May 2016), 28 subjects (13.5%) in the IDL + BR group and 4 subjects (1.9%) in the placebo + BR group had ≥ Grade 3 diarrhoea and/or colitis

In the IDL + BR group, the median (Q1, Q3) time to onset of the first ≥ Grade 3 event of diarrhoea/colitis (N = 28) was 38.6 (11.1, 79.6) weeks, and the median (Q1, Q3) time to resolution of highest grade diarrhoea/colitis (N = 23) was 2.0 (0.9, 4.3) weeks.

In the placebo + BR group, the median (Q1, Q3) time to onset of the first ≥ Grade 3 event of diarrhoea/colitis (N = 4) was 16.4 (10.4, 29.6) weeks, and the median (Q1, Q3) time to resolution of highest grade diarrhoea/colitis (≥ Grade 3) (N = 4) was 0.9 (0.4, 1.8) weeks.

In the IDL + BR group, 4 subjects had their study drug dose reduced, 16 subjects had an interruption in study drug, and 4 subjects discontinued IDL due to ≥ Grade 3 diarrhoea and/or colitis.

In the placebo + BR group, 2 subjects (1.0%) had an interruption in study drug, and no subject had a dose reduction or discontinued the study drug

No deaths due to diarrhoea and/or colitis were reported in this study.

Comment: Data essentially confirm results in prior trials; delayed onset of colitis.

Skin toxicity

Altogether13 subjects (6.3%) in the IDL + BR group and no subject in the placebo+BR group had ≥ Grade 3 rash. Two subjects had their study drug dose reduced, 4 subjects had an interruption in study drug, and 3 subjects discontinued IDL due to ≥ Grade 3 rash.

One death was reported in the IDL + BR group which was attributed to SJS. Subject [redacted] had begun taking acyclovir on Study Day 13 in response to mucosal lesions at 2 anatomical sites and developed papular eruptions and hyperemia of skin, pruritus and fever. She was hospitalized on Study Day 14 and study drug (IDL/placebo) was withdrawn on that day. Three days later the subject was diagnosed with SJS and died on Study Day 28. The investigator assessed the event as unrelated to study drug or BR and potentially associated with acyclovir. Cases of SJS and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported when IDL was administered concomitantly with other medications associated with these syndromes.

On study day 313 a subject developed a rash after recently starting on azithromycin followed by levofloxacin. Additional concomitant medications included acyclovir, furosemide, and omeprazole. A diagnosis of SJS was made and the subject was treated with steroids and the event was considered resolved on Study Day 313.

No case of TEN was reported in this study.

Comment: Skin toxicity including SJS is captured by sections 4.4 and 4.8.

CLL Transformation and Second Malignancies Adjusted for Exposure (Safety Analysis Set)

	IDL + BR (N = 207)			PI + BR (N = 209)		
	Number of Subjects with Events	Drug Exposure at Risk (Person Year)	Incidence Rate per Person Year (95% CI)	Number of Subjects with Events	Drug Exposure at Risk (Person Year)	Incidence Rate per Person Year (95% CI)
CLL Transformation	4	288.9	0.01 (0.0038, 0.0354)	7	213.2	0.03 (0.0132, 0.0676)
Second Malignancies	27	267.1	0.10 (0.0666, 0.1471)	14	207.6	0.07 (0.0369, 0.1132)

Comment: As expected, skin malignancies dominated. There was no increase in number of transformations.

Deaths

In the IDL + BR group, 33 subjects died on study (deaths between randomization and within 30 days following end of study) and 20 subjects died during long-term follow-up.

In the placebo + BR group, 32 subjects died on study and 39 subjects who died during long-term follow-up.

Events were those expected in patients with advanced CLL. The most common events leading to death were pneumonia (2.4% of the IDL + BR group and 2.4% of the placebo + BR group) and sepsis (1.4% of the IDL + BR group and 1.0% of the placebo + BR group).

Comment: No signal

SAEs Reported for ≥ 2% of Subjects in Either Treatment Group (Safety Analysis Set)

Preferred Term, n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)
Number of Subjects (%) with any SAE	147 (71.0)	94 (45.0)
Febrile Neutropenia	43 (20.8)	10 (4.8)
Pneumonia	36 (17.4)	16 (7.7)
Pyrexia	25 (12.1)	11 (5.3)
Sepsis	10 (4.8)	4 (1.9)
Diarrhoea	12 (5.8)	1 (0.5)
Neutropenia	9 (4.3)	3 (1.4)
Anaemia	6 (2.9)	5 (2.4)
Lower Respiratory Tract Infection	6 (2.9)	5 (2.4)
Neutropenic Sepsis	3 (1.4)	6 (2.9)
Respiratory Tract Infection	3 (1.4)	5 (2.4)
Urinary Tract Infection	5 (2.4)	3 (1.4)
Pulmonary Embolism	2 (1.0)	5 (2.4)
Bronchitis	1 (0.5)	5 (2.4)
Septic Shock	5 (2.4)	1 (0.5)
Squamous Cell Carcinoma	1 (0.5)	5 (2.4)

BR = bendamustine + rituximab, IDL = idelalisib, Pl = placebo
AEs were classified by PT using MedDRA version 19.0.
Subjects who experienced multiple events within the same PT were counted once per PT.

Comment: The difference in SAEs is driven by difference in infectious events.

AEs Leading to Study Drug Discontinuation in ≥ 2 Subjects Total (Safety Analysis Set)

Preferred Term, n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)
Number of Subjects (%) with AEs Leading to IDL/Pl Discontinuation	68 (32.9)	31 (14.8)
Pneumonia	11 (5.3)	5 (2.4)
Pyrexia	4 (1.9)	2 (1.0)
Diarrhoea	5 (2.4)	0
Febrile Neutropenia	3 (1.4)	2 (1.0)
Sepsis	3 (1.4)	2 (1.0)
Anaemia	2 (1.0)	1 (0.5)
Colitis	3 (1.4)	0
Hepatocellular Injury	3 (1.4)	0
Neutropenia	3 (1.4)	0
Thrombocytopenia	3 (1.4)	0
Abdominal Pain	2 (1.0)	0
Acute Myocardial Infarction	0	2 (1.0)
Asthenia	0	2 (1.0)
Autoimmune haemolytic anaemia	0	2 (1.0)
Cough	2 (1.0)	0
Lung Adenocarcinoma	1 (0.5)	1 (0.5)
Nausea	2 (1.0)	0
Pancytopenia	2 (1.0)	0
Pneumonia Cytomegaloviral	1 (0.5)	1 (0.5)
Pneumonitis	2 (1.0)	0
Pruritus	1 (0.5)	1 (0.5)
Respiratory Failure	1 (0.5)	1 (0.5)
Respiratory Tract Infection	1 (0.5)	1 (0.5)
Vomiting	2 (1.0)	0

Comment: The overall discontinuation rates are high. Reporting by the induction period IDL/PL+BR vs. the continuation period IDL/PL would be of value **(OC)**

Overall, 16.4% (34 subjects) of the IDL + BR group and 6.2% (13 subjects) of the placebo + BR group had AEs leading to **dose reduction** of study drug (IDL/placebo).

The most frequently reported AEs leading to reduction of study drug were increased ALT (2.9% IDL + BR) and (0.5% placebo + BR) and diarrhoea (3.9% IDL + BR and 0.5% placebo + BR).

All other AEs leading to dose reduction of study drug occurred in ≤ 2% of either treatment group.

Adverse Events Leading to IDL Dose Interruption

Among subjects in the IDL + BR group, 122 of 207 subjects (58.9%) had an AE that led to IDL dose interruption. Adverse events leading to IDL dose interruption reported for ≥ 5% of subjects included diarrhoea (28 subjects, 13.5%), ALT increased (19 subjects, 9.2%), febrile neutropenia (15 subjects, 7.2%), and pneumonia (11 subjects, 5.3%).

Adverse Events Leading to IDL Dose Interruption Reported for ≥ 2%

Preferred Term	IDL + BR (N = 207) n (%)
Subjects with Any AE Leading to IDL Dose Interruption	122 (58.9)
Diarrhoea	28 (13.5)
Alanine Aminotransferase Increased	19 (9.2)
Pneumonia	11 (5.3)
Febrile Neutropenia	15 (7.2)
Pyrexia	9 (4.3)
Aspartate Aminotransferase Increased	10 (4.8)
Neutropenia	8 (3.9)
Colitis	2 (1.0)
Fatigue	2 (1.0)
Rash	5 (2.4)
Transaminases Increased	6 (2.9)
Dehydration	2 (1.0)
Pneumocystis jirovecii Pneumonia	1 (0.5)
Abdominal Pain	1 (0.5)
Sepsis	2 (1.0)
Pneumonitis	1 (0.5)

Assessors comment

According to the protocol of study GS-US-312-0115, if a subject experiences an adverse event that is suspected to be related to study drug (idelalisib/placebo) during the course of study treatment, then study drug administration may be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree. If permanent discontinuation is not required, the study drug may be reinstituted at either the starting dose level (150 mg/dose BID) or at Dose Level -1 (100 mg/dose BID). Rituximab doses will not be modified during the study. If a subject experiences an adverse event that is suspected to be bendamustine-related and requires a dose modification during the course of study therapy, then the bendamustine dose should be reduced by 1 dose level.

The number of subjects with dose discontinuations, dose reductions and interruptions was high with IDL + BR treatment. The median time to the dose interruption and the duration of the dose interruption has not been provided. A subject could have had multiple dose modifications (note: the number of subjects have been reported not the number of events). According to the protocol reescalation of the dose is not needed, even if there is minimal or no toxicity with the reduced dose (at the discretion of the investigator). As such, dose re-escalation was only performed in 9 subjects (4.3%) with IDL + BR in study GS-US-312-0115. It is uncertain to what aspect the dose modifications of IDL + BR have influenced the percentage of expected doses taken and the number of days (or infusions) with treatment.

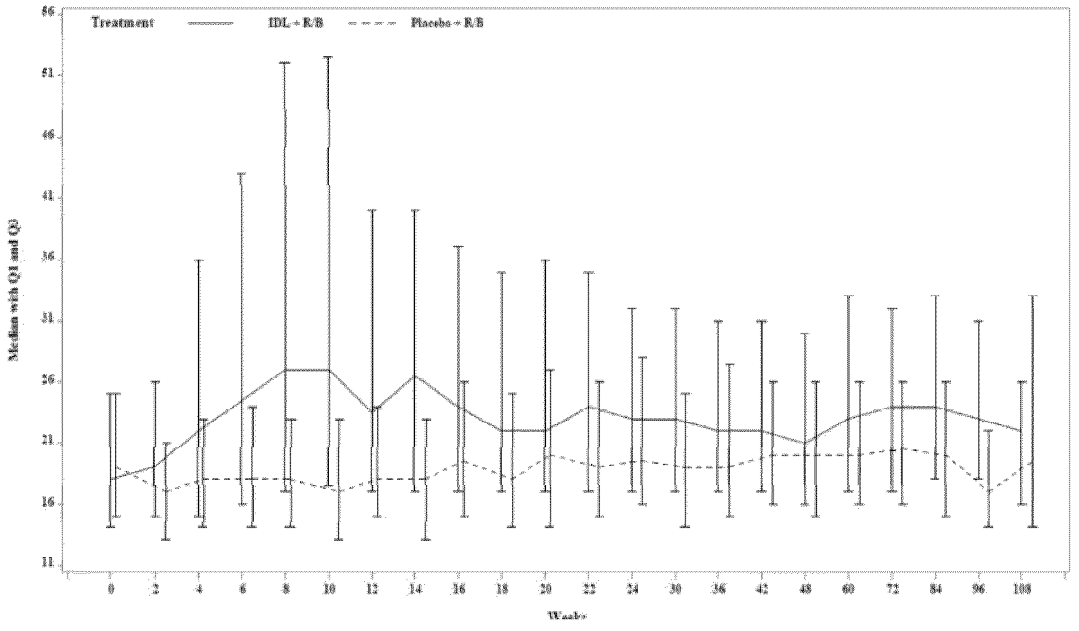
Laboratory findings

Treatment-Emergent Transaminase Elevations (Safety Analysis Set)

	IDL + BR (N = 207) n (%)	Pl + BR (N = 209) n (%)
Subjects with any Grade 3 or 4 ALT or AST Elevation	47 (22.7)	8 (3.8)
Subjects with any Grade 3 or 4 ALT Elevation	44 (21.3)	6 (2.9)
Subjects with any Grade 3 or 4 AST Elevation	32 (15.5)	7 (3.3)
Subjects with any Grade 3 or 4 ALT and AST Elevation	29 (14.0)	5 (2.4)
Resolved to Grade 1 or Less	44 (21.3)	8 (3.8)
Subjects Rechallenged after Dose Interruption	35 (16.9)	4 (1.9)
Rechallenged at 150 mg BID	23 (11.1)	2 (1.0)
Recurrence of Grade 3 or 4 ALT or AST Elevation	5 (2.4)	0
Resolved to Grade 1 or Less	4 (1.9)	0
Rechallenged at 100 mg BID	12 (5.8)	2 (1.0)
Recurrence of Grade 3 or 4 ALT or AST Elevation	4 (1.9)	1 (0.5)
Resolved to Grade 1 or Less	4 (1.9)	0

Comment: The increased frequency in the IDL arm is obvious. Of note, re-challenge at the same dose (150 mg) was successful in 18/23 subjects.

Median (Q1, Q3) ALT (U/L) over Time, Safety Analysis Set



Comment: The gradual increase up to weeks 8-10 followed by a "plateau" on IDL monotherapy is noteworthy.

The around w. 8-10 peak has similarities with the colitis peak and might inform about the underlying mechanisms.

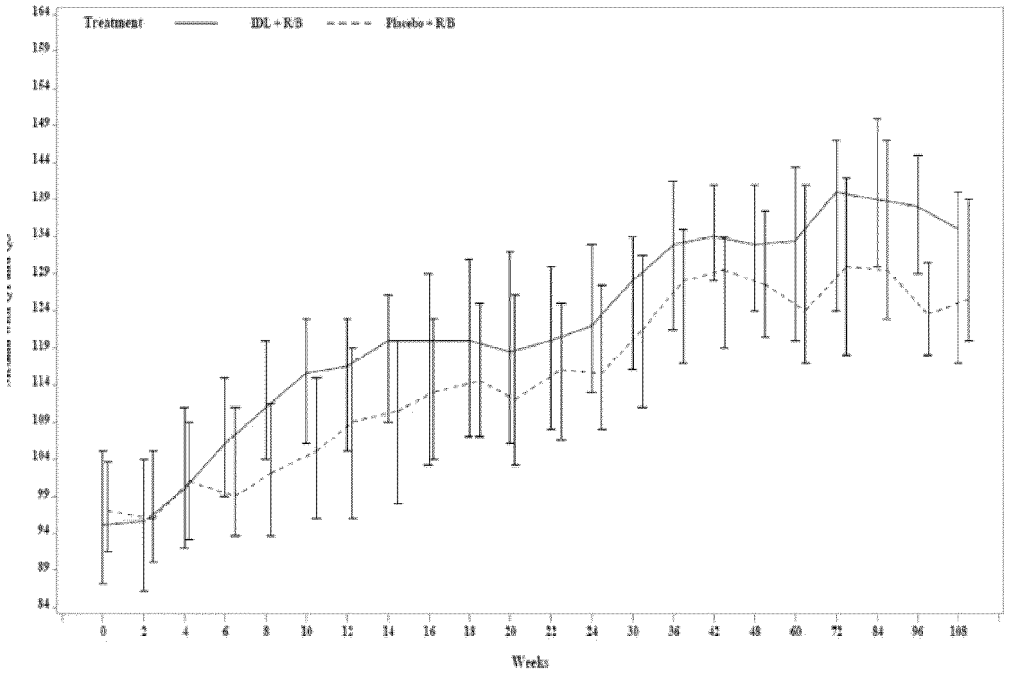
Haematology

BR and IDL+BR are undoubtedly myelosuppressive, as demonstrated in the overviews of ARs, at the same time response to therapy is associated with haematological improvement in case of CLL-related haematotoxicity. This is illustrated here by the shift table for IDL+BR and the figure below.

Shift from Baseline to worst CTCAE Severity Grade Safety Analysis Set, Haemoglobin

	IDL + R/B Baseline Severity Grade [a]						
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing	Total
Parameter: Hemoglobin (Anemia)	97	68	35	7	0	0	207
Worst Grade [b]							
Grade 0	23 (23.7%)	1 (1.5%)	0	0	0	0	24 (11.6%)
Grade 1	46 (47.4%)	33 (48.5%)	3 (8.6%)	0	0	0	82 (39.6%)
Grade 2	18 (18.6%)	19 (27.9%)	15 (42.9%)	5 (71.4%)	0	0	57 (27.5%)
Grade 3	10 (10.3%)	14 (20.6%)	17 (48.6%)	2 (28.6%)	0	0	43 (20.8%)
Grade 4	0	0	0	0	0	0	0
Missing	0	1 (1.5%)	0	0	0	0	1 (0.5%)

Median (Q1, Q3) Hemoglobin (g/L) over Time (Safety Analysis Set – Subjects with Abnormality at Baseline and at Least 1 Postbaseline Measurement)



Treatment-Emergent Hematologic Abnormalities

Neutropenia (all grades) was the most common treatment-emergent hematologic abnormality overall, occurring in 89.9% (186 subjects) of the IDL + BR group and in 90.0% (188 subjects) of the placebo + BR group. Grade 3 or 4 neutropenia was observed in 72.9% (151 subjects) of the IDL + BR group and in 63.2% (132 subjects) of the placebo + BR group.

GS-US-312-0115: Summary of Treatment-Emergent Hematology Abnormalities In Either Treatment Group, Subjects with Any Disease Type or Therapy Regimen.

Parameter[a], n (%)	IDL + BR (N = 207)	Pl + BR (N = 209)
Hemoglobin Decreased (Anaemia)		
Any Grade	124 (59.9)	130 (62.2)
≥ Grade 3	41 (19.8)	36 (17.2)
Lymphocyte Count Increased		
Any Grade	8 (3.9)	9 (4.3)
≥ Grade 3	5 (2.4)	4 (1.9)
Lymphocyte Count Decreased		
Any Grade	155 (74.9)	144 (68.9)
≥ Grade 3	103 (49.8)	94 (45.0)
Neutrophil Count Decreased		
Any Grade	186 (89.9)	188 (90.0)
≥ Grade 3	151 (72.9)	132 (63.2)
Platelet Count Decreased		
Any Grade	105 (50.7)	108 (51.7)
≥ Grade 3	42 (20.3)	35 (16.7)
Leukocytes (White Blood Cell Decreased)		
Any Grade	169 (81.6)	167 (79.9)
≥ Grade 3	94 (45.4)	91 (43.5)

BR = bendamustine + rituximab, IDL = idelalisib, Pl = placebo
a Worst grade at post baseline; baseline was the last observation on or before the first dose of study drug.
Grades were obtained per CTCAE version 4.03.
Source: Section 15.1, Table 8.2.2

The most commonly observed (> 10% incidence) Grade 3 or 4 hematologic laboratory abnormalities included the following: neutrophil count decreased (39.6%), lymphocyte count decreased (33.4%), leukocytes decreased (22.3%), and platelet count decreased (11.5%) (table 62, Summary of clinical safety).

Treatment-Emergent Neutropenia

Among subjects with any disease type or therapy regimen (N = 1952), the incidence of treatment-emergent neutropenia laboratory abnormalities of any grade was 61.6%, and the incidence of Grade 3 or 4 events was 39.6% (ISS Table 8.2.4). The median time to onset for Grade 3 or 4 neutropenia was 1.6 months, with a KM estimate of median time to resolution of 3.9 weeks (ISS Table 8.15.4). Among subjects with CLL in Studies GS-US-312-0115, GS-US-312-0116, and GS-US-312-0119, the incidence of treatment-emergent neutropenia laboratory abnormalities of any grade was high and similar between the IDL + BR and placebo + BR groups, with 89.9% and 90.0% of subjects in the respective groups having treatment-emergent neutropenia. The incidence of neutropenia laboratory abnormalities of any grade was lower in the IDL + R, placebo + R, IDL + O, and O alone groups, occurring in 63.6%, 55.6%, 72.8%, and 58.1% of subjects, respectively. The incidence of Grade 3 or 4 treatment-emergent neutropenia in the IDL + BR group was higher than in the placebo + BR group, with 72.9% and 63.2% of subjects in the respective groups having such events. The incidence of Grade 3 or 4 treatment-emergent neutropenia was lower in the IDL + R, placebo + R, IDL + O, and O alone groups, occurring in 41.8%, 29.6%, 49.1%, and 32.6% of subjects, respectively. The prevalence of Grade 3 or 4 treatment-emergent neutropenia was generally highest during the first 12 weeks on study and decreased thereafter.

Incidence of Laboratory Abnormalities of Neutropenia, Subjects with CLL in Studies GS-US-312-0115, GS-US-312-0116, and GS-US-312-0119

	IDL + BR (N = 207)	BR (N = 209)	IDL + R (N = 110)	R (N = 108)	IDL + O (N = 173)	O (N = 86)
Neutropenia, n (%)						
Any Change Postbaseline	186 (89.9)	188 (90.0)	70 (63.6)	60 (55.6)	126 (72.8)	50 (58.1)
Any Grade 3 or 4	151 (72.9)	132 (63.2)	46 (41.8)	32 (29.6)	85 (49.1)	28 (32.6)
Grade 3	45 (21.7)	62 (29.7)	26 (23.6)	18 (16.7)	37 (21.4)	13 (15.1)
Grade 4	106 (51.2)	70 (33.5)	20 (18.2)	14 (13.0)	48 (27.7)	15 (17.4)

IDL + BR = IDL + bendamustine + rituximab in Study GS-US-312-0115; BR = placebo + bendamustine and rituximab in Study GS-US-312-0115;
IDL + R = IDL + rituximab in Study GS-US-312-0116; R = placebo + rituximab in Study GS-US-312-0116; IDL + O = IDL + ofatumumab in Study GS-US-312-0119;
O = ofatumumab alone in Study GS-US-312-0119

Treatment-emergent lab abnormality = abnormality worsening by ≥ 1 grade compared with baseline from first treatment dose to 30 days after last dose.

For subjects in Study GS-US-312-0116 who received open-label IDL, treatment-emergent lab abnormality = abnormality worsening by ≥ 1 grade compared with baseline from first study treatment dose to the day before the first dose of open-label IDL.

Source: ISS Table 8.2.1

Assessors comment

It is noticed that a significant proportion of patients in IDL + BR and BR arm have treatment-emergent haematological abnormalities, although this is to be expected in subjects with CLL, inclusion criteria were set for adequate neutrophil and platelet counts as well as Hb level. With respect to neutropenia the incidence in de BR based regimens is increased compared to R or O based regimen including the grade 3-4 neutropenia. It is known that haematologic toxicities occur with bendamustine treatment in CLL such as neutropenia, thrombocytopenia, and anaemia, however, the triple combination IDL + BR increases the risk for grade 4 neutropenia.

GS-US-312-0115: Summary of Treatment-Emergent Serum Chemistry Abnormalities: Events with Any Occurrence of ≥ Grade 3 Severity

Parameter*, n (%)	IDL + BR (N = 207)	PI + BR (N = 209)
Albumin Decreased		
Any Grade	48 (23.2)	30 (14.1)
≥ Grade 3	3 (1.4)	0
Alkaline Phosphatase Increased		
Any Grade	78 (37.7)	44 (21.1)
≥ Grade 3	3 (1.4)	0
ALT Increased		
Any Grade	131 (63.3)	67 (32.1)
≥ Grade 3	44 (21.3)	6 (2.9)
AST Increased		
Any Grade	111 (53.6)	61 (29.2)
≥ Grade 3	32 (15.5)	7 (3.3)
Bilirubin Increased		
Any Grade	49 (23.7)	38 (18.2)
≥ Grade 3	1 (0.5)	2 (1.0)
Albumin-Corrected Calcium Increased		
Any Grade	6 (2.9)	6 (2.9)
≥ Grade 3	1 (0.5)	0
Albumin-Corrected Calcium Decreased		
Any Grade	11 (5.3)	21 (10.0)
≥ Grade 3	3 (1.4)	2 (1.0)
Cholesterol High		
Any Grade	18 (8.7)	5 (2.4)
≥ Grade 3	1 (0.5)	0
Creatinine Increased		
Any Grade	14 (6.8)	23 (11.0)
≥ Grade 3	0	0
Creatinine Clearance Decreased		
Any Grade	57 (27.5)	63 (30.1)
≥ Grade 3	1 (0.5)	0

Blood chemistry laboratory abnormalities ≥ Grade 3 observed in ≥ 5% of subjects with any disease type or therapy regimen (N = 1952) in either treatment group, are summarized in the above. The most commonly observed (> 10% incidence) Grade 3 or 4 chemistry laboratory abnormalities were phosphate decreased (in IDL+BR only), ALT increased and AST increased. ALT increase and AST increase was also observed in the cohort 'subjects with any disease type or therapy regimen'.

There are no new physical findings or other unreported observations related to safety in this supplemental application.

Assessors comment

Patients with ongoing hepatitis, liver cirrhosis, portal hypertension, or liver injury were excluded from study GS-US-312-0115 and thus constitute an area of missing information.

The laboratory abnormalities in relation to idelalisib exposure should be further elucidated with respect to potassium, albumin and phosphate.

Special populations

Age

In the pivotal Study GS-US-312-0115, an additional analysis of ADRs, defined as AEs assessed by the investigator as related to treatment with IDL, was performed for subjects who received IDL + BR treatment in 3 age groups: < 65 (N = 131), 65 to < 75 (N = 60), and 75 to < 85 (N = 16) years of age. The overall incidence of ADRs was similar across the 3 age groups. Categories of ADRs with a higher incidence in the oldest age group (75 to < 85 years of age) compared with either of the 2 younger age groups were as follows:

All serious ADRs: < 65 years (45 subjects, 34.4%), 65 to < 75 years (20 subjects, 33.3%), 75 to < 85 years (10 subjects, 62.5%)

Fatal serious ADRs: < 65 years (2 subjects, 1.5%), 65 to < 75 years (1 subject, 1.7%), 75 to < 85 years (1 subject, 6.3%)

AEs leading to drop-outs (study drug withdrawn): < 65 years (19 subjects, 14.5%), 65 to < 75 years (11 subjects, 18.3%), 75 to < 85 years (4 subjects, 25.0%)

Infections and infestations SOC: < 65 years (28 subjects, 21.4%), 65 to < 75 years (15 subjects, 25.0%), 75 to < 85 years (9 subjects, 56.3%)

Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, and fractures: < 65 years (2 subjects, 1.5%), 65 to < 75 years (1 subject, 1.7%), 75 to < 85 years (1 subject, 6.3%)

Comment: The IDL+BR regimen appears poorly tolerated in patients >75 years of age, but the sample is very small.

There were no apparent gender or race related differences.

Cross-study comparison

Adverse Events ≥ Grade 3 selected by the assessor in Studies GS-US-312-0115, GS-US-312-0116, and GS-US-312-0119 (Safety Analysis Set)

Preferred Term	IDL + BR (N = 207) n (%)	PI + BR (N = 209) n (%)	IDL + R (N = 110) n (%)	PI + R (N = 108) n (%)	IDL + O (N = 173) n (%)	O Alone (N = 86) n (%)
Subjects with Any ≥ Grade 3 AE	196 (94.7)	163 (78.0)	81 (73.6)	58 (53.7)	160 (92.5)	48 (55.8)
Pneumonia	29 (14.0)	17 (8.1)	11 (10.0)	10 (9.3)	28 (16.2)	7 (8.1)
Febrile Neutropenia	49 (23.7)	13 (6.2)	5 (4.5)	5 (4.6)	21 (12.1)	3 (3.5)
Diarrhoea	25 (12.1)	4 (1.9)	10 (9.1)	0	41 (23.7)	1 (1.2)
Alanine Aminotransferase Increased	22 (10.6)	1 (0.5)	4 (3.6)	0	14 (8.1)	0
Sepsis	12 (5.8)	6 (2.9)	6 (5.5)	3 (2.8)	13 (7.5)	1 (1.2)
Colitis	3 (1.4)	0	5 (4.5)	0	14 (8.1)	0
Infusion Related Reaction	5 (2.4)	4 (1.9)	0	4 (3.7)	5 (2.9)	1 (1.2)
Aspartate Aminotransferase Increased	11 (5.3)	0	1 (0.9)	0	6 (3.5)	0

Preferred Term	IDL + BR (N = 207) n (%)	PI + BR (N = 209) n (%)	IDL + R (N = 110) n (%)	PI + R (N = 108) n (%)	IDL + O (N = 173) n (%)	O Alone (N = 86) n (%)
Urinary Tract Infection	5 (2.4)	4 (1.9)	1 (0.9)	2 (1.9)	6 (3.5)	0
Neutropenic Sepsis	3 (1.4)	6 (2.9)	2 (1.8)	0	4 (2.3)	2 (2.3)
Pneumonitis	4 (1.9)	0	4 (3.6)	1 (0.9)	8 (4.6)	0
Pneumocystis jirovecii pneumonia	2 (1.0)	0	4 (3.6)	1 (0.9)	9 (5.2)	0
Septic Shock	5 (2.4)	1 (0.5)	0	2 (1.9)	5 (2.9)	1 (1.2)
Transaminases Increased	8 (3.9)	0	3 (2.7)	1 (0.9)	2 (1.2)	0
Rash	6 (2.9)	0	1 (0.9)	0	5 (2.9)	1 (1.2)
Respiratory Tract Infection	3 (1.4)	5 (2.4)	0	1 (0.9)	2 (1.2)	2 (2.3)
Autoimmune Haemolytic Anaemia	0	5 (2.4)	0	0	1 (0.6)	0
Rash Maculo-Papular	1 (0.5)	0	1 (0.9)	0	4 (2.3)	0

2.3.3.11. Discussion on clinical safety (Rapporteur)

Qualitatively there are no new adverse reactions identified, but quantitatively there is a non-trivial increase in adverse reactions grade ≥3 and SAEs compared with BR.

Any SAE is thus increased from 45 to 70%, grade ≥3 events from 78 to 95%. AEs leading to IDL/placebo discontinuation were reported in 33% vs. 15%. Data on dose reductions/discontinuations with respect to BR will be asked for.

Grade ≥3 infectious events were increased from 26 to 41%. Skin, diarrhoea and hepatic events were also relevantly increased. The events of pneumocystis or CMV infectious events, however, were low in both treatment arms. Adherence to prophylactic measures should be discussed.

To increase the understanding, AEs should be reported separately for BR+IDL and BR+PI for the period of combination therapy and IDL and placebo during the maintenance period.

2.3.3.12. Conclusions on clinical safety

IDL+BR cannot be characterised as a well-tolerated CLL regimen, but the SPC is considered to provide reasonable guidance.

2.3.3.13. CoRapp Safety Discussion:

The safety evaluation to expand the CLL indication for Zydelig to include its use in combination with bendamustine and rituximab (BR) is based on the results of the primary analysis of pivotal Study GS-US-312-0115 and supported by data from other IDL monotherapy or combination therapy studies (combination with rituximab or ofatumumab). Study GS-US-312-0115 was stopped early as recommended by the DMC based on efficacy of the formal interim analysis (at 75% of the PFS events). Demographics and baseline characteristics in study GS-US-312-0115 represent an elderly fit CLL population. In comparison to the other combination therapy studies (GS-US-312-0116, and GS-US-312-0119), study GS-US-312-0115 set out specific inclusion criteria for haematopoietic laboratory parameters (ANC ≥ 1.5 10 9/L, platelets ≥75 10 9/L and Hb ≥10 g/dl).

In study GS-US-312-0115 the type of AEs reported >10% of subjects are in line with what is expected from the studied population (CLL), the use of IDL, bendamustine, and/or rituximab, e.g. gastrointestinal AEs, myelosuppression, infusion related and infection related AEs. In the IDL + BR arm 23.7% of subjects reported febrile neutropenia (compared to 6.2% in BR alone), even when adjusted for exposure duration the incidence rate for febrile neutropenia was increased compared to BR alone (adjusted incidence rate 0.20 (IDL+BR) versus 0.06).

The combination of idelalisib with bendamustine rituximab gives rise to grade 3 AEs (94.7%) and SAEs (71.0%). This is reflected in high rates of dose interruption and frequently give rise to dose modifications (dose interruptions, dose reduction or dose discontinuation). Serious AEs were reported for 71.0% in the IDL + BR group compared to 45% in the placebo + BR group. The preferred terms with >5% of subjects were febrile neutropenia (IDL + BR 20.8%), pneumonia (IDL + BR 17.4%), pyrexia (IDL + BR 12.1%).

A slightly higher frequency of on study deaths was observed in the IDL + BR arm compared to BR, 25 of 207 subjects (12.1%) in the IDL + BR group and 22 of 209 subjects (10.5%) in the placebo + BR group died while receiving treatment or within 30 days of the last dose of treatment. In comparison, death due to an AE was reported for IDL + R 3.6% and IDL + O 15%. Deaths due to PD were not reported as AEs or SAEs. Adverse events leading to death reported for > 1 subject were mainly in the SOC infections and infestations, e.g. pneumonia (5 subjects, 2.4%), sepsis (3 subjects, 1.4%), and septic shock (2 subjects, 1.0%).

It is noticed that a significant proportion of patients in IDL + BR and BR arm have treatment-emergent haematological abnormalities, although this could be expected in subjects with CLL, inclusion criteria were set for adequate neutrophil and platelet counts as well as Hb level. It is known that hematologic toxicities occur with bendamustine treatment in CLL such as neutropenia, thrombocytopenia, and anaemia. For subjects with CLL in Studies GS-US-312-0115, GS-US-312-0116, and GS-US-312-0119, the incidence of treatment-emergent neutropenia laboratory abnormalities of any grade was high and similar between the IDL + BR and placebo + BR groups, with 89.9% and 90.0% of subjects in the respective groups having treatment-emergent neutropenia. The incidence of Grade 3 or 4 treatment-emergent neutropenia in the IDL + BR group was higher than in the placebo + BR group, with 72.9% and 63.2%. Neutrophil count monitoring is recommended in the SmPC. In the event of severe neutropenia, treatment should be interrupted and may be restarted at a lower dose upon resolution. Noticeable, dose interruption due to neutropenia was only reported in 3.9%, whereas discontinuations or dose reductions were reported <2% of the cases.

The identified risks for idelalisib treatment, including transaminase elevations, severe diarrhoea/colitis, pneumonitis, neutropenia, and rash, were generally more frequently seen in the idelalisib + BR arm compared to BR alone. In study GS-US-312-0115, 28 subjects (13.5%) in the IDL + BR group and 4 subjects (1.9%) in the placebo + BR group had ≥ Grade 3 diarrhoea and/or Colitis. It appears that the majority of ≥ Grade 3 Diarrhoea and/or Colitis could be resolved with a dose reduction or dose interruption.

Severe infections (≥ Grade 3) were observed in a large proportion of the patients, e.g. 52.2% IBR and 28.7% BR (study GS-US-312-0115) including 14 death in IDL+BR and 10 death in BR due to infections. Following the safety signal, the AEI list was expanded to include additional infection terms (specifically ≥ Grade 3 infection, ≥ Grade 3 febrile neutropenia, any grade CMV infection, and any grade PJP) and the protocol was amended to included mandated prophylaxis for PJP, CMV surveillance and increased monitoring. In study GS-US-312-0115, 7 subjects (3.4%) in the IDL + BR group and 2 subjects (1.0%) in the placebo + BR group had pneumonitis (any grade). Even so, 4 subjects (1.9%) in the IDL + BR group (no subject in placebo + BR) had PJP of any grade. One subject [redacted]

had PJP infection while receiving PJP prophylaxis (within 4 weeks of start prophylaxis). In study GS-US 312-0115: 13 subjects (6.3%) in the IDL + BR group and 3 subjects (1.4%) in the placebo + BR group had CMV of any grade.

The number of subjects with dose discontinuations, dose reductions and interruptions due to AEs was high with IDL + BR treatment (respective 32.9%, 16,4%, and 58,9%). The main AEs (≥5%) leading to dose modification were pneumonia, ALT increase, febrile neutropenia, and diarrhoea with IDL + BR treatment. The median time to and duration of the dose interruption has not been provided. A subject could have had multiple dose modifications. According to the protocol reescalation of the dose is not needed, even if there is minimal or no toxicity with the reduced dose (at the discretion of the investigator). As such, dose re-escalation was only performed in 9 subjects (4.3%) with IDL + BR in study GS-US-312-0115. It is uncertain to what aspect the dose modifications of idelalisib + BR have influenced the percentage of expected doses taken compared to the actual dosages taken, as this reflects the tolerability of the treatment. Moreover, it is not known how many AEs leading to dose modification where due to bendamustine toxicity.

Analysis of safety data by age group (< 65, 65 to < 75, and 75 to < 85), revealed no clear differences for younger or older subjects in the duration of exposure to IDL+BR, as well as in the rates of AEs, SAEs, or AEs leading to IDL discontinuation or death. A separate safety analysis for IDL+BR treatment in 17p patients was not performed.

2.3.3.14. CoRapp conclusion on clinical safety

In general, the safety findings of idelalisib combined with bendamustine rituximab are consistent with the known safety profile of idelalisib, when combined with rituximab or ofatumumab in previously treated CLL patients. No new safety issues have been raised. The most frequently reported AEs assessed by the investigator as related to study drug (IDL + BR) were neutropenia, diarrhoea, and alanine aminotransferase increased.

The tolerability of IDL+BR gives rise to dose reductions or drug discontinuation due to AEs and high incidence rates of ≥grade 3 AEs and SAEs even in a generally more fit (e.g. younger with a shorter disease duration) study population in Study GS-US-312-0115 than subjects in Studies GS-US-312-0116 and GS-US-312-0119. Although a head-to-head comparison with IDL + R has not been performed, it appears that the addition of bendamustine to IDL+R leads to increased toxicity.

2.3.4. PSUR cycle

The PSUR cycle remains unchanged.

2.3.5. Direct Healthcare Professional Communication

Not warranted

2.3.6. Update of SmPC

Refer to appended SmPC

2.3.7. Risk management plan

RMP version 2.2 is dated 23 January 2017.

Summary Table of Safety Concerns

Important Identified Risks	Transaminase elevation
	Severe diarrhoea/colitis
	Pneumonitis
	Neutropenia
	Rash
	Stevens-Johnson syndrome – Toxic epidermal necrolysis
	Serious infections including opportunistic infections such as PJP and CMV
	Off-label use (first line CLL therapy in patients without 17p deletion/*TP53* mutation, early line iNHL therapy)
Important Potential Risks	Reproductive toxicity including teratogenicity
	Drug-drug interaction with CYP3A inducers
	Drug-drug interaction with CYP3A substrates
	Photosensitivity
	Skin cancer
Missing Information	Development of drug resistance
	Carcinogenicity
	Long-term safety
	Safety in patients with severe hepatic impairment
	Safety in patients with severe renal impairment
	Safety in patients with chronic active hepatitis
	Safety in patients with concomitant immunization
	Immunological effects and auto-immunity
	Safety in children
	Safety of breastfeeding
	Drug-drug interaction with oral contraceptive

Comment: For important identified risks; rash and SJS may be replaced with "Severe toxic skin reactions, including SJS and TEN" and replace transaminase elevations with "severe transaminase elevations", similarly neutropenia with "severe neutropenia".

Please refer to appended SmPC and leaflet.

2.3.8. User consultation

A justification for not performing a user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable by the Rapporteur and Co-rapporteur.

Justification submitted by the MAH:

"This change includes only a very minor alteration in wording to reflect the new combination of idelalisib with bendamustine and rituximab and does not significantly impact the readability of the package leaflet. In accordance with this assessment, readability testing has not been performed on the package leaflet submitted in this variation."

2.3.9. Quick Response (QR) code

N.a.

3. Benefit-Risk Balance

Proposed indication: *Zydelig is indicated in combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received at least one prior therapy*.

A single pivotal study has been submitted in support of the claimed indication. Patients with resistant or refractory CLL who had been exposed to a purine analogue and an anti-CD20 MoAb were enrolled and the study compared IDL vs. placebo on top of BR followed by IDL or placebo until progression, etc. Patients with del17p/*TP53* positive disease were enrolled, but BR background is considered acceptable as the study was initiated in 2012.

Benefits

The aims of treatment of CLL include improved survival and a reduction in disease-related signs and symptoms such as cytopenias and B-symptoms. ORR and PFS benefits are likely to reflect at least symptomatic benefit.

Beneficial effects

With respect to ORR and PFS (primary e.p.), study data appear convincing. The ORR rates were 70 vs. 45% and as regards PFS the HR was 0.33 ($p<0.0001$) with a median difference of about 10 months (21 vs. 11 months) at event rates of 40 and 70%. Improvements in cytopaenia were also demonstrated.

Uncertainty in the knowledge about the beneficial effects

Due to the design, maintenance IDL vs. placebo (and the toxicity profile), benefit beyond PFS1 is essential and OS obviously remains the most convincing outcome measure. The event rate in the OS analysis, however, was only about 30% and the p-value borderline (0.036, HR 0.66).

In response to the LoI an updated analysis with cut-off 31 March 2017 was submitted. At event rates of 36 and 41 %, the HR increased to 0.8 at a p-value 0.2.

Survival data were mainly gathered off-study and a "missingness" analysis was requested. Based on the May 2016 cut-off it was found that 30 patients out of 84 individuals (36%) eligible for long-term follow up (LTFU) declined participation or left TFU in the idelalisib arm vs. 24/116 (21%) in the control group.

PFS2 data were also submitted and the results were seemingly favourable, HR 0.57. In the IDL arm, however, the percentage of deaths was 81% and in the control 64% (q7). Furthermore in 40% and 30% of patients are reported as next-line "unknown" (vs. next-line yes or no)

Risks

This is an add-on study to an acceptable background therapy in patients likely to tolerate BR. Thus the risk is confined to adverse reactions.

Unfavourable effects

There is a clinically relevant increase in SAEs and grade ≥3 events, especially infectious events (please refer to table below) and the discontinuation rates due to AEs are high (IDL 33%, placebo 15%).

Uncertainty in the knowledge about the unfavourable effects

To improve the understanding there is a need to separate the "induction" phase from the "maintenance" phase.

Effects Table

			Uncertainties/ Strength of evidence	References
Favourable Effects				
OS (02 May 2016)	**IDL + BR (N = 207)**	**PI + BR (N = 209)**	Borderline statistically significant Immature Uncertainty about missingness in follow-up after end of study	Study report
Number (%) of Subjects with Events	53 (25.6)	70 (33.5)		
KM Estimate of OS (Months)[a]				
Q1 (95% CI)	23.5 (16, NR)	15.7 (13.2, 20.3)		
Median (95% CI)	NR (NR, NR)	40.6 (31.6, NR)		
Adjusted HR (95% CI)[b]	0.67 (0.47, 0.96)			
P-value from Stratified Log-Rank Test	0.036			
OS (31 March 2017)	**IDL + BR (N = 207)**	**PI + BR (N = 209)**	Note shift in HR and loss of "significance" Data unstable, i.e. still immature. In the idelalisib arm 30/84 patients eligible for long term follow-up did not participate in LTFU In the control corresponding figures were 24/116	
Number (%) of Subjects with Events	75 (36.2)	86 (41.1)		
KM Estimate of OS (Months)[a]				
Q1 (95% CI)	21.4 (15.2; 27.5)	15.7 (13.2, 20.3)		
Median (95% CI)	NR (40.1, NR)	43.1 (38.4, NR)		
Adjusted HR (95% CI)[b]	0.8 (0.59; 1.09)			
P-value from Stratified Log-Rank Test	0.20			
PFS (07 October 2015)	**IDL + BR (N = 207)**	**PI + BR (N = 209)**	Convincing	
Number (%) of Subjects with Events	84 (40.6)	149 (71.3)		
Disease Progression	60 (29.0)	130 (62.2)		

			Uncertainties/ Strength of evidence	References
Death	24 (11.6)	19 (9.1)		
KM Estimate of PFS (Months)[a]				
Median (95% CI)	20.8 (16.6, 26.4)	11.1 (8.9, 11.1)		
At 24 weeks	88.5 (83.0, 92.3)	82.1 (76.0, 86.7)		
At 48 weeks	75.0 (68.0, 80.6)	50.5 (43.2, 57.5)		
Adjusted HR (95% CI)[b]	0.33 (0.25, 0.44)			
P-value[c]	6.540×10^{-16}			
ORR (07 October 2015)	**IDL + BR (N = 207)**	**Pl + BR (N = 209)**	Convincing Note small proportion of CR	
Best Overall Response, n (%)[a]				
Complete Response (CR)	3 (1.4)	0		
Partial Response (PR)	142 (68.6)	93 (44.5)		
Progressive Disease (PD)	1 (0.5)	19 (9.1)		
ORR (CR+CRi+PR)	145 (70.0)	94 (45.0)		
95% CI[c]	63.3, 76.2	38.1, 52.0		
Unfavourable Effects (02 May 2016)				
Adverse Events ≥ Grade 3				
Preferred Term	IDL + BR (N = 207) n (%)	Pl + BR (N = 209) n (%)	Clinically relevant increase in severe ADRs. High discontinuation rates	
Subjects with AE≥ Grade 3	197 (95.2)	163 (78.0)		
Any SAE	149 (72.0)	94 (45.0)		
AE IDL/placebo discontinuation	83 (40.1)	31 (14.8)		
AE leading to death	27 (13.0)	19 (9.1)		
Number of subjects (%) with dose reductions of IDL/placebo due to AE.	35 (16.9)	13 (6.2)		
Pneumonia	29 (14.0)	17 (8.1)		
Febrile Neutropenia	49 (23.7)	13 (6.2)		
Diarrhoea	25 (12.1)	4 (1.9)		
Alanine Aminotransferase Increased	22 (10.6)	1 (0.5)		
Sepsis	12 (5.8)	6 (2.9)		
Colitis	3 (1.4)	0		

			Uncertainties/ Strength of evidence	References
Pneumonitis	4 (1.9)	0		
***Pneumocystis jirovecii* pneumonia**	2 (1.0)	0		
Septic Shock	5 (2.4)	1 (0.5)		
Rash	6 (2.9)	0		

Benefit-Risk Balance

C.I.6. Extension of indication of Zydelig in combination with Bendamustine and rituximab in patients with relapsed CLL

In order to outbalance the clinically relevant increase in ≥ Grade 3 infectious events, hepatic events, colitis and skin toxicity as reflected in the high discontinuation rate in the IDL arm and apparent increase in deaths, reliable and stable OS data are needed for a proper B/R assessment. Reliability, however, is questioned due to missing data in long term follow-up and maturity is questioned due to the shift in OS HR from 0.66 to 0.8.

As the meaning of progression on maintenance differs from progression on placebo, favourable outcome data beyond PFS1 are needed. Submitted PFS2 data are at this stage non-interpretable (see above). Time to first and second next-line therapy may provide some reassurance as regards benefit beyond PFS1.

- **Following the assessment of the extension of indication, the benefit/risk was considered negative.**
- **In response to the second list of outstanding issues, the application for the extension of indication for Zydelig (idelalisib) in combination with bendamustine and rituximab for the treatment of adult patients with relapsed chronic lymphocytic leukemia (CLL) has been withdrawn by the MAH**.

C.I.13. Submission of interim report from study 101-08: a Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of idelalisib in Combination with Rituximab in Elderly Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Monotherapy may seem rather poorly tolerated in elderly treatment naïve CLL patients not assumed to tolerate chemotherapy (22% discontinued due to diarrhea/colitis). This, however, should be put in context of durable activity, median PFS > 2 years. Infectious events and causality are hard to assess in the absence of a control group. Monotherapy is clearly very active.

- This submission fulfils PAM 008 adopted during the initial MAA.

Submission of the final report from study GS-US-312-0123: a phase 3 randomized study evaluating idelalisib in combination with bendamustine and rituximab (IDL+BR) vs. Pl+BR in subjects with previously untreated CLL.

This study was terminated early due to a safety signal (EPAR EMEA/H/A-20/1439/C/003843/0023, July 2016, article 20 procedure). Due to early study termination, the pre-specified efficacy analyses were not conducted.

The idelalisib development program experience to date does not support a by-line, overall increased add-on toxicity. The underlying mechanism for the increased early infectious events and associated fatalities seen in the idelalisib front-line CLL studies does not appear attributable to a single identified factor (eg severe neutropenia, decreased CD4+ counts, con-committant bendamustine administration), but is more likely due to heightened immunomodulatory effects experienced by some patients with a treatment-naïve immune system.

- Following the withdrawal of the extension of indication (C.I.6) and assessment of the submissions under C.I.13 - the overall B/R of Zydelig remains positive.

4. Recommendations

The following application has been withdrawn by the MAH in response to the second list of outstanding issues:

Variation withdrawn		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6. Extension of Indication: Extension of the approved chronic lymphocytic leukemia (CLL) indication for Zydelig to include its use in combination with bendamustine and rituximab based on the results of the primary analysis of pivotal Study GS-US-312-0115 "a Phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukemia" as a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 2.2 has also been submitted. After withdrawal of C.I.6, based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

C.I.13: Submission of the final report from study 101-08, a phase 2, single-arm study evaluated idelalisib monotherapy and in combination with rituximab in elderly subjects with previously untreated CLL or small lymphocytic lymphoma. Inclusion of this report provides additional safety data to support the evaluation of the use of idelalisib in patients with CLL. Submission of this report is also made in

fulfilment of PAM008.

C.I.13: Submission of the final report from study GS-US-312-0123, a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab in subjects with previously untreated CLL. Inclusion of this report is supportive of a complete safety evaluation concerning the use of this combination in patients with CLL.

Annex 1: 1st Request for supplementary information

Clinical pharmacology aspects

Other concerns

1. A discussion on potential DDI of Bendamustine with idelalisib and rituximab, supported by a presentation of the pharmacokinetics from the 2 different arms in study GS-US-312-0115 should be provided by the MAH.

Clinical efficacy aspects

Other concerns

2. Due to the toxicity of IDL add-on to BR and the maintenance phase comparing IDL with placebo, as mature as possible survival data within this procedure are considered essential for the proper assessment of benefit-risk. Fully acknowledging that the event rate over time is low, nevertheless please submit a survival update.
3. After end of study, survival data were collected every 6 months. Please provide details as regards patients not accepting to be included in the survival follow-up and missing data in relation to the data cut-off.
4. Part of the pivotal study population previously received BR treatment (14.5% in the IDL + BR arm, 8.1% in the placebo arm). According to current treatment guidelines, first line treatment may be repeated if the relapse or progression occurs at least 24-36 months after chemo-immunotherapy and if the 17p deletion was excluded. Information as regards last prior regimen prior to enrolment should be provided. If bendamustine was part of the last prior regimen, please discuss the activity of the study regimens in these patients. This is of special relevance in case of too early re-treatment (within e.g. 24 months).
5. The applicant is asked to discuss whether this was the case in patients previously treated with BR.
6. Please provide data on time from PD to next-line therapy.
7. To further substantiate the efficacy of IDL+ BR, the applicant is asked to present PFS2 data, if available, or time to next subsequent and second subsequent therapy if not, as well as the type of subsequent other anticancer therapies.
8. Please resubmit the forest plots including also medians (for the EPAR).
9. If data on MRD were collected, please report.
10. The proposed indication is for patients "who have received at least one prior therapy". However, most included patients received 2 or more prior treatments, and the applicant is requested to present the proportion of patients that received only 1 prior therapy.
11. In section 4.2 of the SmPC it is recommended to reduce the dose to 100 mg twice daily after a dose interruption. The applicant is asked to explain why a large percentage of patients that interrupted study treatment was rechallenged at a dose level of 150 mg BID, and to discuss the frequency of further dose modifications and treatment discontinuations after rechallenge. The median time to dose interruption, the number of dose interruptions per subject, and the

duration of the dose interruption should be provided. The applicant should discuss whether the presented efficacy results are still representative for the 150 mg twice daily dose taking into account the percentage of expected doses to be taken and the number of days (or infusions) with treatment.

12. The applicant is asked to present and discuss PFS KM curves for patients with or without 17p deletion and/or TP53 mutation. The applicant is furthermore asked to discuss the observed differences in PFS and OS results between the 17p deletion patient group and the 17p deletion and/or TP53 mutation patient group.

13. In 12.9% of placebo treated patients (vs. 0% in the IDL + BR treatment group) the reason for study discontinuation was study wide unblinding. It is not known why this occurred, and whether the blinding was sufficiently preserved throughout the study. The applicant is asked to elaborate.

14. Disposition of patients has been presented several times by the applicant, with slightly different frequencies. The applicant is asked to clarify which data regarding the patient flow in study GS-US-312-0115 is correct.

15. The applicant stated that 75% of PFS events had occurred at the time of the interim analysis, which exceeds the planned frequency of 66%. Based on the number of events presented in Table 'Primary Endpoint: PFS by IRC Assessment, 07 October 2015 (ITT), the actual frequency of PFS events seemed to be lower (56%). The applicant is asked to clarify.

16. The applicant stated that an increase of 10 points in Karnofsky Perfomance Status (KPS) has been observed for the IDL + BR treated patients. This would be similar to the 10 points increase observed with IDL + R alone. However, based on the median scores provided in Table 15 (baseline 90, best change from baseline/highest value 90), an improvement of 0 points is expected, as is the case for the placebo + BR treated patients. The applicant is asked to clarify.

17. Efficacy results in study GS-US-312-0115 have been presented for patients <65 and ≥65 years of age, safety results have been presented for *3 age* groups: (< 65 (N = 131), 65 to < 75 (N = 60), and 75 to < 85 (N = 16) years of age). Since the median age of the intended target population is relatively high, the applicant is asked to present efficacy results for these 3 age groups as well.

18. The per protocol analysis set was added to the pivotal study protocol as an amendment in Dec 2012. However, results of the pre-specified sensitivity analyses with the PP analysis set for the primary and secondary endpoints were not presented, and the applicant is asked to submit these data and discuss whether results were comparable to the ITT analysis set.

19. In the study report of the pivotal study, the applicant stated that a separate biomarker analysis plan will be prepared to detail pharmacodynamics and biomarker analyses. Biomarker results, however, could not be found in the dossier and the applicant is requested to submit information regarding disease-associated biomarkers, and to discuss potential mechanisms of resistance to IDL, based on published and in house data, e.g. in relation to PI3K mutation status.

20. PI3K mutations have been reported in a number of malignancies (Chaloub Ann Rev Pathol 2009). Please discuss if this is a concern in the treatment with IDL that would justify assessing PI3K status in patients with resistance to IDL.

21. Is there a difference in baseline characteristics in the IDL+BR arm between patients with events of PFS ≤6 months, >6 months and ≤18 months and > 18 months? To contextualise, similar data may be reported for the Pl+BR arm.

22. The applicant is asked to present results of the objective health resource utilization associated with the addition of IDL to BR, as these results could not be found.

Clinical safety aspects

Other concerns

23. Safety data should be reported separately for the induction phase (IDL/placebo +BR) and the maintenance phase (IDL vs. placebo). This should include the reporting of ≥grade 3 events, dose reductions, interruptions and discontinuation for all drugs separately and if combined (IDL, placebo, bendamustine and rituximab).

24. Please provide details as regards adherence to PJP and CMV prophylaxis.

25. Adverse reactions led to the stopping of all first-line studies. Please compare adverse events of special interest per 2 months period IDL+BR vs. BR in studies 0015 and 0023. Please also discuss whether there is a "true" increase in add-on toxicity related to line of therapy and if so if there are underlying mechanisms making this plausible.

26. In the protocol of study GS-US-312-0115 it was stated (in the section of dose modifications) that tumour lysis syndrome (TLS) had occurred in 5% of subjects treated with idelalisib in combination with bendamustine or bendamustine rituximab. In the safety summary and in the interim CSR of study GS-US-312-0115 no cases of TLS have been reported. The applicant is requested to clarify.

27. It has not been reported whether cases of overdose in study GS-US-312-0115 have occurred. If so, narratives should be provided.

28. The laboratory abnormalities observed in study GS-US-312-0115 related to IDL + BR exposure should be further elucidated with respect to potassium, albumin and phosphate.

29. Neutrophil count monitoring is recommended in the SmPC. In the event of severe neutropenia, treatment should be interrupted and may be restarted at a lower dose upon resolution. Noticeable, dose interruption due to neutropenia was only reported in 3.9%, whereas discontinuations or dose reductions were reported <2% of the cases. As such the applicant is requested to report what measures where taken to address the severe cases of neutropenia (e.g. concomitant medication) and to what extent these cases resolved spontaneously.

30. Data cut-off for the interim study report of study GS-US-312-0115 was 02 May 2016, as such a full update of safety from study GS-US-312-0115, including patients in long-term follow-up, is requested.

31. Is there a relationship between degree of neutropenia and onset of pneumonia, colitis and pyrexia?

RMP

Other concerns

32. Please revise the safety concerns:

For important identified risks; rash and SJS may be replaced with "Severe toxic skin reactions, including SJS and TEN" and replace transaminase elevations with "severe transaminase elevations", similarly neutropenia with "severe neutropenia".

Assessment of the responses to the 1st Request for Supplementary Information

Clinical pharmacology aspects

Other concerns

Question 1
A discussion on potential DDI of Bendamustine with idelalisib and rituximab, supported by a presentation of the pharmacokinetics from the 2 different arms in study GS-US-312-0115 should be provided by the MAH.

Summary of MAH answer
The Study GS-US-312-0115 Protocol (Amendment 9) included the following secondary objective: to characterize the effect of bendamustine and rituximab (BR) on IDL exposure through evaluations of IDL plasma concentrations over time. No analysis of bendamustine or rituximab was planned, as no drug-drug interactions (DDIs) were anticipated based on in vitro studies. Bendamustine is primarily metabolized by cytochrome P450 (CYP) 1A2 via hydrolysis to 2 minor metabolites with low activity. IDL does not inhibit CYP1A2, thus is not anticipated to affect the metabolism of bendamustine. Therefore, bendamustine plasma concentrations were not evaluated. Idelalisib is primarily metabolized by aldehyde oxidase (AO) and CYP3A4. Bendamustine is not a CYP3A4 inhibitor and is not anticipated to affect the metabolism of IDL through that pathway. However, the possible interaction of bendamustine with AO is unknown; therefore, the potential effect of bendamustine on IDL pharmacokinetics (PK) was evaluated in this study. Plasma samples were collected predose and at 1.5 hours postdose on Days 1, 29, 57, 85, 113, 141, and 169. Concentrations of IDL were determined using a validated high performance liquid-chromatography-tandem mass spectrometry bioanalytical method. Plasma concentrations were comparable at predose and 1.5 hours postdose between Week 4 and Week 24 (Table 1). In addition, trough concentrations of IDL were comparable to those observed in other studies (eg, Studies 101-02, GS-US-312-0116, and GS-US-312-0119) and to population PK modeling estimates following monotherapy with 150 mg IDL twice daily. These results are consistent with the lack of effect of BR coadminis on IDL PK. Thus it is unlikely that bendamustine interacts with AO in this context. Rituximab is a protein, and therefore does not use the same mechanisms of clearance as small molecules, and is not expected to interact with IDL, as was previously established in clinical Study 101-07.

Table 1 **GS-US-312-0115: Idelalisib Plasma Concentrations Following 150 mg Idelalisib Twice Daily in Combination with Bendamustine and Rituximab in Previously Treated Subjects with Chronic Lymphocytic Leukemia (PK Analysis Set)**

	Sampling Time					
	Week 4		Week 12		Week 24	
IDL (ng/mL)	Predose	1.5 Hours Postdose	Predose	1.5 Hours Postdose	Predose	1.5 Hours Postdose
N	153	169	140	150	105	117
Median (Q1, Q3)	363.0 (221.0, 633.0)	2040.0 (1280.0, 2600.0)	330.0 (187.5, 546.0)	1995.0 (1450.0, 2610.0)	317.0 (184.0, 578.0)	2100.0 (1380.0, 2790.0)

Source: GS-US-312-0115 Interim 1 CSR Table 10-1

Rapporteur

The MAH has provided a discussion on potential DDI of Bendamustine with idelalisib and rituximab. In short, Rituximab is a protein, and therefore does not use the same mechanisms of clearance as small molecules, and is not expected to interact with IDL. Bendamustine is metabolized by cytochrome P450 (CYP) 1A2 and IDL does not inhibit CYP1A2, thus is not anticipated to affect the metabolism of bendamustine. Idelalisib is primarily metabolized by aldehyde oxidase (AO) and CYP3A4. Bendamustine is not a CYP3A4 inhibitor but Bendamustines effect on aldehyde oxidase is not known. Therefore, study GS-US-312-0115 secondary objective was to characterize the effect of BR on IDL exposure through evaluations (presented in table 1 above). Plasma concentrations were comparable at predose and 1.5 hours postdose between Week 4 and Week 24 and trough concentrations of IDL were comparable to those observed in other studies.

Overall the discussion provided by the applicant is acceptable and it is unlikely that there is a potential for relevant DDI of Bendamustine with idelalisib and rituximab.

Issue resolved

3. Clinical efficacy aspects

Other concerns

Question 2

Due to the toxicity of IDL add-on to BR and the maintenance phase comparing IDL with placebo, as mature as possible survival data within this procedure are considered essential for the proper assessment of benefit-risk. Fully acknowledging that the event rate over time is low, nevertheless please submit a survival update. (Rapp + CoRapp)

Summary of MAH answer

Overall survival (OS) data in this report were estimated for the Intent-to-Treat (ITT) Analysis Set based on a data cutoff date of 31 March 2017 (median follow-up of 31 months) and are presented in Table 3. and Figure 2. OS data presented in the Study GS-US-312-0115 Interim 1 clinical study report (CSR) with a data cutoff date of 02 May 2016 (median follow-up of 21 months) are also presented in Table 3. and Figure 2 for comparison. The ITT Analysis Set included all subjects who were randomized in the study with treatment group designated according to initial randomization. Data from surviving subjects were censored at the last time that the subject was known to be alive on study or in long-term follow-up (LTFU). Initiation of new anti-cancer therapy was allowed during LTFU and more subjects in the placebo arm received new therapy compared to the IDL arm, which also contributed to the dilution of the comparison.

Between the data cutoff date for the Interim 1 CSR (02 May 2016), and the data cutoff date for this report (31 March 2017), 38 deaths were reported: 22 deaths in the idelalisib plus bendamustine and rituximab (IDL + BR) group and 16 deaths in the placebo plus bendamustine and rituximab

(placebo + BR) group. By that date, 161 subjects had died: 75 subjects (36.2%) in the IDL + BR group and 86 subjects (41.1%) in the placebo + BR group. The adjusted hazard ratio (HR) (95% confidence interval [CI]) for OS was 0.8 (0.59, 1.09). The median OS of the IDL + BR group remained not reached, while the median OS of the placebo + BR group changed from 40.6 months to 43.1 months.

Table 2 GS-US-312-0115: Overall Survival (ITT Analysis Set)

	IDL + BR (N = 207)	PI + BR (N = 209)
31 March 2017 Data Cutoff Date		
Number (%) of Subjects with Events	75 (36.2)	86 (41.1)
Death	75 (36.2)	86 (41.1)
Number (%) of Subjects Censored	132 (63.8)	123 (58.9)
Discontinued Study	90 (43.5)	116 (55.5)
Ongoing in Study	42 (20.3)	7 (3.3)
KM Estimate of OS (Months)[a]		
Q1 (95% CI)	21.4 (15.2, 27.5)	15.7 (13.2, 20.3)
Median (95% CI)	NR (40.1, NR)	43.1 (38.4, NR)
Q3 (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI)[b]	0.8 (0.59, 1.09)	
P-value from Stratified Log-Rank Test	1.995×10^{-1}	
P-value from Unstratified Log-Rank Test	2.782×10^{-1}	
02 May 2016 Data Cutoff Date		
Number (%) of Subjects with Events	53 (25.6)	70 (33.5)
Death	53 (25.6)	70 (33.5)
Number (%) of Subjects Censored	154 (74.4)	139 (66.5)
Discontinued Study	84 (40.6)	116 (55.5)
Ongoing in Study	70 (33.8)	23 (11.0)
KM Estimate of OS (Months)[a]		
Q1 (95% CI)	23.5 (16, NR)	15.7 (13.2, 20.3)
Median (95% CI)	NR (NR, NR)	40.6 (31.6, NR)
Q3 (95% CI)	NR (NR, NR)	NR (40.6, NR)
Adjusted HR (95% CI)[b]	0.67 (0.47, 0.96)	
P-value from Stratified Log-Rank Test	3.637×10^{-2}	
P-value from Unstratified Log-Rank Test	5.874×10^{-2}	

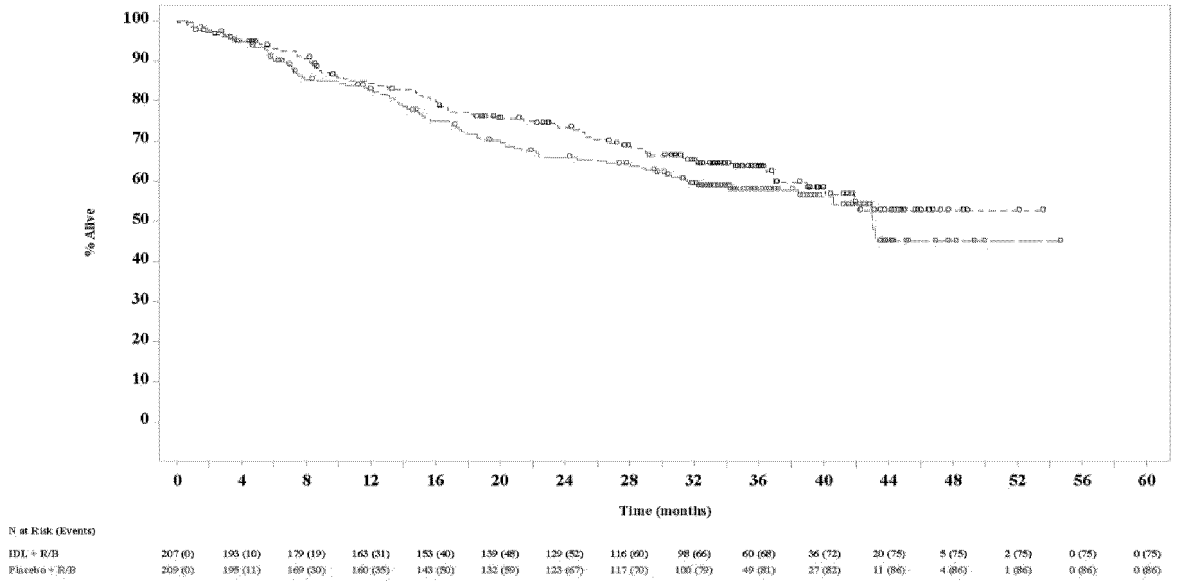
CI = confidence interval; HR = hazard ratio; IDL + BR = idelalisib plus bendamustine and rituximab; KM = Kaplan-Meier; NR = not reached; OS = overall survival; PI + BR = placebo plus bendamustine and rituximab; Q1 = first quartile; Q3 = third quartile

a OS (months) = (date of death – date of randomization + 1) / 30.4375.

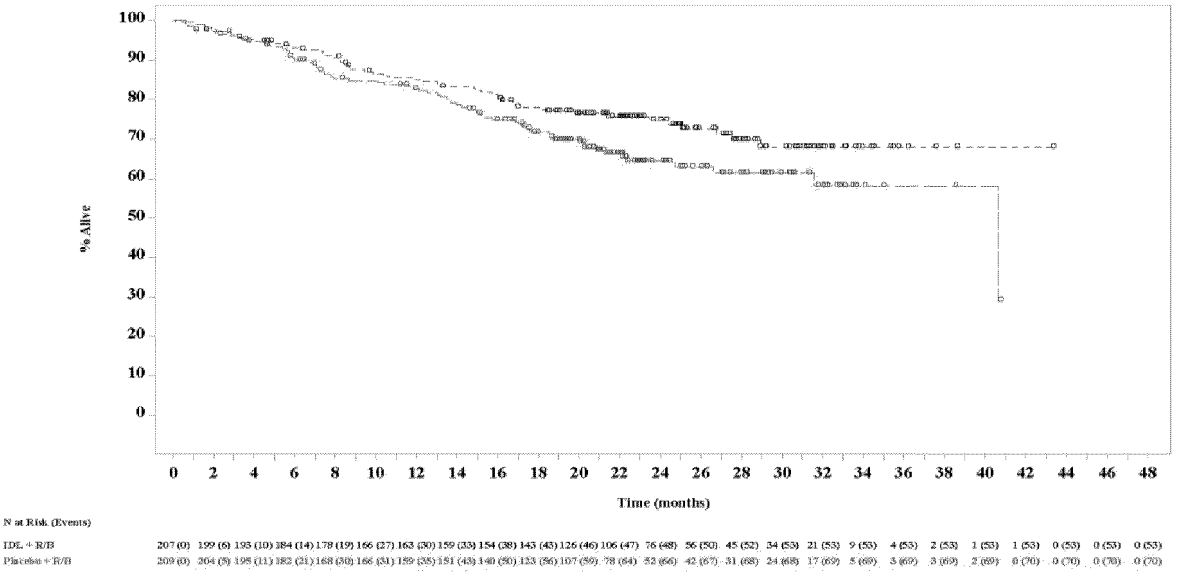
b Hazard ratios and 95% CIs were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation status, and disease status).

Source: CHMP Table 2.1 and GS-US-312-0115 Interim 1 CSR Table 9-5

Figure 2 GS-US-312-0115: Kaplan-Meier Plots of Overall Survival Based on Database Cutoff Date: 31 March 2017 (ITT Analysis Set)



Database cutoff date: 02 May 2016 (ITT Analysis Set)



Rapporteur (SE)

At event rates of 36 and 41% and a change in the OS HR from 0.67 (95% CI 0.47; 0.96) in the prior OS analyses to 0.8 (95% CI 0.59; 1.09) data appear unstable and are moving in a non-favorable direction. This constitutes a major concern from a benefit/risk perspective.

Not resolved

Co-Rapporteur (NL)

It is agreed with the Rapporteur that the unfavourable change in point estimates of HR with the updated OS analysis is of concern and should be discussed by the applicant. Despite the change from significant to a non-significant difference in OS between the treatment arms, the change in the KM curves is considered subtle, and seems mostly related to the right part of the curves, in which only few patients were at risk for an OS event.

To investigate the impact further, it is suggested that the discussion should at least include the following: 1) the period of clear benefit i.e more than 5% difference in the Kaplan-Meier curves extends from 16-31 months in the 02MAY2016 analysis to 16-36 months in the 31MAR2017 analysis, but after that survival curves are similar between 37-43 month. In that period, however, only 10-15% of patients are at risk, so no conclusions about similarity (loss of efficacy of IDL+BR) in that period can be drawn. The Applicant is asked to investigate whether the shift in point estimates of the HR from 0.67 to 0.8 could be caused by this 37-43 months period. 2) As noted in the response to RSI#14, Gilead stopped the study early due to efficacy and treatment assignments were unblinded study-wide on 16 November 2015. The Applicant is asked to report whether cross-over of patients in the placebo arm crossed over to the experimental arm and if so, discuss its impact. 3) The impact of informative censoring on OS is requested to be investigated by additional analyses, not only the possible informative censoring within 26 (IDL+BR) vs 19 (placebo + BR) patients that did not enter the long term follow-up but also for the 4 (IDL+BR) vs 6 (placebo+BR) subjects, that discontinued during the long-term follow-up (see also RSI#3 Rapp). 4) The applicant should indicate when final OS data could be expected as the estimated study completion data was Dec 2017, and present the data as soon as possible.

The by the Rapporteur raised uncertainty due to informative censoring (not entering LTFU or lost from LTFU) is acknowledged and should be investigated. Although this possibly informative censoring is substantial with 36 vs 21% of the discontinued patients in the experimental and the control arm (30/84 IDL+BR and 25/116 placebo+BR), it represents "only" 12% and 11%, respectively from the total study population (25/207 and 22/209).

In conclusion, we support the Rapporteurs request for additional discussion regarding unfavourable updated OS data in a major objection, and we propose that the discussion should include at least the 4 topics highlighted above.

Issue not resolved

Question 3
After end of study, survival data were collected every 6 months. Please provide details as regards patients not accepting to be included in the survival follow-up and missing data in relation to the data cut-off.
Summary of response

Overall Survival and Long-Term Follow-Up Status Based on Data Through 02 May 2016 (ITT Analysis Set)

	IDL + BR (N = 207)	PI + BR (N = 209)
Number (%) of Subjects with Events	53 (25.6)	70 (33.5)
Death during LTFU	20 (9.7)	38 (18.2)
Death on Study	33 (15.9)	32 (15.3)
Number (%) of Subjects Censored	154 (74.4)	139 (66.5)
Ongoing in Study	70 (33.8)	23 (11.0)
Discontinued Study	84 (40.6)	116 (55.5)
Discontinued Study, No LTFU	26 (12.6)	19 (9.1)
Discontinued Study, Entered LTFU	58 (28.0)	97 (46.4)
Ongoing in LTFU	54 (26.1)	91 (43.5)
Discontinued during LTFU	4 (1.9)	6 (2.9)
KM Estimate of OS (Months)[a]		
Q1 (95% CI)	23.5 (16.0, NR)	15.7 (13.2, 20.3)
Median (95% CI)	NR (NR, NR)	40.6 (31.6, NR)
Q3 (95% CI)	NR (NR, NR)	NR (40.6, NR)
Adjusted HR (95% CI)[b]	0.67 (0.47, 0.96)	
P-value from Stratified Log-Rank Test	3.637×10^{-2}	
P-value from Unstratified Log-Rank Test	5.874×10^{-2}	

LTFU = long-term follow-up

Reasons for Study Discontinuation, Subjects Who Did Not Enter Long-Term Follow-Up (ITT Analysis Set)

Subject Disposition	IDL + BR (N = 26) n (%)	PI + BR (N = 19) n (%)	Total (N = 45) n (%)
Reason for Study Discontinuation			
Adverse Event	5 (19.2)	3 (15.8)	8 (17.8)
Physician Decision	0	4 (21.1)	4 (8.9)
Withdrawal by Subject	10 (38.4)	7 (36.8)	17 (37.8)
Progressive Disease	6 (23.1)	5 (26.3)	11 (24.4)
Noncompliance with Study Drug	2 (7.7)	0	2 (4.4)
Other	1 (3.8)	0	1 (2.2)
Other Anticancer/Experimental Therapy	1 (3.8)	0	1 (2.2)
Lost to Follow-Up	1 (3.8)	0	1 (2.2)

Rapporteur

In the idelalisib arm, 26 patients who discontinued the study did not participate in long term follow up (LTU) and an additional 4 individuals left LTU meaning that altogether 30/84 or 36% of patients eligible for LTU are not available for OS follow-up.

Corresponding figures for the control arm were 19 + 5, i.e. 24/116, 21%.

Of note these figures are not meant for comparison between study arms only to highlight that missingness is an issue. Data notably refer to the May 2016 cut-off.

Missingness is by default not a random phenomenon and may be related to prognosis.

Not resolved

Question 4
Part of the pivotal study population previously received BR treatment (14.5% in the IDL + BR arm, 8.1% in the placebo arm). According to current treatment guidelines, first line treatment may be repeated if the relapse or progression occurs at least 24-36 months after chemo-immunotherapy and if the 17p deletion was excluded. Information as regards last prior regimen prior to enrolment should be provided. If bendamustine was part of the last prior regimen, please discuss the activity of the study regimens in these patients. This is of special relevance in case of too early re-treatment (within e.g. 24 months).
Summary of response

When Study GS-US-312-0115 was initiated, the treatment guidelines from September 2011 were not as specific as the current guidelines quoted in the question. In the Study GS-US-312-0115 Interim 1 CSR, 37 subjects (17.9%) in the IDL + BR group reported bendamustine as part of the most common prior regimen, compared with 22 subjects (10.5%) in the placebo + BR group.

Bendamustine was reported to be the last regimen prior to study entry for 25 subjects (12.1%) in the IDL + BR group and 13 subjects (6.2%) in the placebo + BR group.

Comparison of Confirmed BOR for Subjects Without 17p Deletion who Received Bendamustine in Last Regimen Prior to Treatment with IDL + BR or Placebo + BR (ITT Analysis Set)

Subject Treatment Group	Number of Subjects	Study GS-US-312-0115			
		PR	SD	PD	NE
IDL + BR	20	15 (75.0%)	4 (20.0%)	0	1 (5.0%)
Placebo + BR	11	4 (36.4%)	5 (45.5%)	2 (18.1%)	0

Most of the subjects in Study GS-US-312-0115 received 2 or more prior therapy regimens before study entry. Only 2 subjects met the criteria of relapse or progression occurring 24 to 36 months after initial chemoimmunotherapy when the 17p deletion was excluded. No subjects without a 17p deletion had disease progression < 24 months after initial chemoimmunotherapy. Both subjects achieved BOR of PR to treatment with IDL + BR, but the sample size was too small to draw any meaningful conclusions.

Rapporteur:

Use of BR as last prior regimen was more common in the experimental arm, i.e. the experimental arm was not favoured by the use of BR in the last prior regimen. It is also acknowledged that treatment guidelines have changed since the study was initiated, i.e. are stricter in relation to re-treatment.

Resolved.

Question 5

The applicant is asked to discuss whether this was the case in patients previously treated with BR. (CoRapp)

Summary of MAH answer

Data for the subset of subjects referred to in this question, those who had BR as part of any prior regimen before entry into Study GS-US-312-0115 but had no 17p deletion, are shown in Table 9 for in the IDL + BR group, and Table 10 for the placebo + BR group. There were 24 subjects (11.6%) in the IDL + BR group and 13 subjects (6.2%) in the placebo + BR group with no 17p deletion who had received BR as part of any regimen prior to entry into Study GS-US-312-0115 (Table 11). Thus, the IDL + BR group had more subjects who had already failed to respond to BR than the placebo + BR group. Nineteen subjects (79.2%) had a BOR of PR to treatment with IDL + BR, compared with only 6 subjects (46.2%) achieving BOR of PR in the placebo + BR group, even though the IDL + BR group had more subjects that did not previously respond to BR alone.

Table 9. **GS-US-312-0115: Subset of Subjects Without 17p Deletion Treated with Bendamustine + Rituximab as Part of Any Regimen Prior to Study Entry and Treated with IDL + BR on Study (ITT Analysis Set)**

Subject	Regimen Number	Regimen Type	Regimen Start/ End Date	PD Date (Prior Regimen)	Study GS-US-312-0115		
					PFS (Months)	OS (Months)	Confirmed BOR
[redacted]	1	BR	15 Feb 2010 / 22 June 2010	March 2012	25.0 (Censor)	25.0 (Censor)	PR
	2	BR	18 April 2011 / 07 Sept 2011	27 May 2013	13.8 (Event)	16.0 (Event)	PR
	2	BR	09 Jan 2012 / 16 July 2012	30 April 2013	6.0 (Event)	24.4 (Event)	SD
	3	BR	18 July 2011 / 13 Oct 2011	11 April 2013	28.5 (Censor)	29.0 (Censor)	PR
	2	BR	01 Jan 2011 / 01 July 2011	28 June 2013	25.1 (Censor)	25.8 (Censor)	PR
	2	BR	25 Feb 2010 / 04 August 2010	30 Nov 2012	11.3 (Event)	18.4 (Censor)	PR
	3	BR	16 October 2011 / 13 March 2012	Oct 2012	5.5 (Censor)	18.1 (Censor)	PR
	5	BR	12 Oct 2009 / 09 Sept 2010	28 Jan 2013	8.8 (Event)	13.1 (Event)	PR
	2	BR	01 Jan 2005 / 01 Jan 2005	2006	30.3 (Event)	30.3 (Censor)	PR
	3	BR	01 Jan 2012 / 21 June 2012	25 Nov 2013	19.5 (Event)	20.8 (Censor)	PR
	6	BR	01 August 2011 / 01 August 2011	August 2011	5.7 (Censor)	6.4 (Censor)	SD
	4	BR	12 March 2012 / 07 August 2012	29 August 2013	19.2 (Censor)	19.4 (Censor)	PR
	3	BR	07 Dec 2011 / 20 March 2012	Oct 2012	19.7 (Censor)	19.7 (Censor)	PR
	2	BR	01 June 2011 / 22 Dec 2011	31 Dec 2012	25.3 (Censor)	25.3 (Censor)	PR
	5	BR	07 June 2012 / 13 Sept 2012	May 2014	13.8 (Censor)	13.8 (Censor)	PR
	1	BR	01 Jan 2011 / 01 Jan 2011	10 April 2013	21.8 (Event)	27.3 (Censor)	PR
	3	BR	08 Mar 2013 / 05 August 2013	May 2014	4.2 (Event)	10.2 (Censor)	SD
	2	BR	02 August 2011 / 29 Feb 2012	28 Nov 2013	0.0 (Censor)	9.4 (Event)	NE
	3	BR	25 Feb 2010 / 17 May 2010	2013	17.4 (Censor)	18.5 (Censor)	PR
	3	BR	25 April 2011 / 26 Sept 2011	11 June 2013	13.9 (Censor)	19.9 (Censor)	PR
[redacted]	2	BR	18 June 2012 / 08 Nov 2012	03 Feb 2014	13.8 (Censor)	13.9 (Censor)	PR
	5	BR	01 Jan 2013 / 25 April 2013	24 Feb 2014	4.6 (Censor)	10.6 (Censor)	SD
	5	BR	18 July 2013 / 19 July 2013	–	16.5 (Censor)	17.2 (Censor)	PR
	5	BR	19 Dec 2012 / 25 April 2013	25 Oct 2013	13.6 (Event)	16.6 (Censor)	PR

Source: CHMP Listing 4.2

Table 10. **GS-US-312-0115: Subset of Subjects Without 17p Deletion Treated with Bendamustine + Rituximab as Part of Any Regimen Prior to Study Entry and Treated with Placebo + BR On Study (ITT Analysis Set)**

Subject	Regimen Number	Regimen Type	Regimen Start/ End Date	PD Date (Prior Regimen)	Study GS-US-312-0115		
					PFS (Months)	OS (Months)	Confirmed BOR
[redacted]	4	BR	20 Sept 2011 / 11 Nov 2011	18 Feb 2014	8.3 (Event)	18.2 (Censor)	PR
	2	BR	19 June 2012 / 06 Nov 2012	14 Feb 2014	11.6 (Event)	14.3 (Censor)	SD
	3	BR	03 April 2010 / 30 Sept 2010	27 Oct 2011	11.2 (Event)	14.8 (Censor)	PR
	4	BR	26 May 2010 / 17 Sept 2010	01 Nov 2012	14.3 (Event)	32.3 (Censor)	PR
	3	BR	10 July 2009 / 15 Dec 2009	August 2012	2.9 (Censor)	25.2 (Censor)	SD
	4	BR	21 May 2012 / 08 Oct 2012	22 July 2013	2.7 (Event)	3.6 (Event)	PD
	4	BR	18 Feb 2011 / 19 July 2011	10 April 2012	8.5 (Censor)	13.9 (Censor)	SD
	2	BR	01 Jan 2011 / 01 Jan 2011	Feb 2012	3.0 (Censor)	12.6 (Event)	SD
	4	BR	01 Dec 2011 / 20 April 2012	19 Feb 2013	6.2 (Event)	7.1 (Event)	PR
	2	BR	01 Jan 2011 / 01 June 2011	Oct 2012	14.9 (Event)	17.2 (Event)	PR
	4	BR	18 Sept 2013 / 28 Nov 2013	16 April 2014	8.5 (Event)	16.8 (Censor)	SD
	5	BR	02 June 2010 / 28 July 2010	29 March 2011	5.7 (Event)	5.7 (Event)	SD
	5	BR	17 Jan 2012 / 29 May 2012	–	16.6 (Censor)	16.6 (Censor)	PR

Source: CHMP Listing 4.2

Table 11. GS-US-312-0115: Comparison of Confirmed BOR for Subjects Without 17p Deletion Treated with Bendamusine + Rituximab as Part of Any Regimen Prior to Study Entry (ITT Analysis Set)

Subject Treatment Group	Number of Subjects	Study GS-US-312-0115			
		PR	SD	PD	NE
IDL + BR	24	19 (79.2%)	4 (16.7%)	0	1 (4.1%)
Placebo + BR	13	6 (46.2%)	6 (46.2%)	1 (4.1%)	0

Source: CHMP Listing 4.2

Co-Rapporteur

This question 5 should be seen in conjunction with OC 4. Only 2 patients met the criteria of relapse or progression occurring 24 to 36 months after initial chemoimmunotherapy when the 17p deletion was excluded. No patients without a 17p deletion had disease progression <24 months after initial chemoimmunotherapy. However, as stated before, it is acknowledged that treatment guidelines have changed since the study was initiated, i.e. are stricter in relation to re-treatment. Moreover, it is reassuring that in the patients that previously received BR treatment, 19 patients (79.2%) had a BOR of PR to treatment with IDL + BR, compared with only 6 patients (46.2%) achieving BOR of PR in the placebo + BR group, even though the IDL + BR group had more subjects that did not previously respond to BR alone.

Issue resolved.

Question 6.

Please provide data on time from PD to next-line therapy.

Summary of response

Seventy subjects in the IDL + BR group and 146 subjects in the placebo + BR group had Independent Review Committee (IRC)-confirmed PD. Twenty-nine (41.4%) of the subjects in the IDL + BR group and 89 (61.0%) of the subjects in the placebo + BR group received next-line therapy. The distribution of time (days) from PD to next-line therapy is skewed to the right in the placebo + BR group, while the IDL + BR group shows widely scattered distribution (Figure 2). The median (Q1, Q3) time from PD to next-line therapy was 81 (36, 218) days for subjects in the IDL + BR group and 109 (45, 204) days for subjects in the placebo + BR group.

Summary of Time (Days) from Progressive Disease to Next-Line Therapy (ITT Analysis Set)

	IDL + BR (N = 207)	**Placebo + BR (N = 209)**
Subjects with PD, n (%)	70 (33.8)	146 (69.9)
Treated with Next-line Therapy, n (%)[a]		
Yes	29 (41.4)	89 (61.0)
No	13 (18.6)	13 (8.9)
Unknown	28 (40.0)	44 (30.1)
Time (Days) from PD to Next-line Therapy		
N	28	89
Mean (StD)	147.2 (144.14)	141.4 (119.04)

Median	80.5	109.0
Q1, Q3	36, 218	45, 204
Minimum, Maximum	11, 443	1, 557

StD = standard deviation
a Percentage was based on the number of subjects with PD

Rapporteur

Immature data in combination with missingness make further analyses meaningless.

Will not be further pursued.

Question 7

To further substantiate the efficacy of IDL+ BR, the applicant is asked to present PFS2 data, if available, or time to next subsequent and second subsequent therapy if not, as well as the type of subsequent other anticancer therapies. ~~as well as the type of subsequent other anticancer therapies~~. (CoRapp)

Summary of MAH answer

Progression-free survival on second-line therapy (PFS2) is defined as the time from randomization to the date of disease progression on next-line treatment or death from any cause. Because the date of objective disease progression on the next-line therapy was not collected in the study, the starting date of the second next-line therapy is used as a proxy. Table 4 summarizes PFS2 based on data through 02 May 2016 and the KM plot is presented in Figure 3.

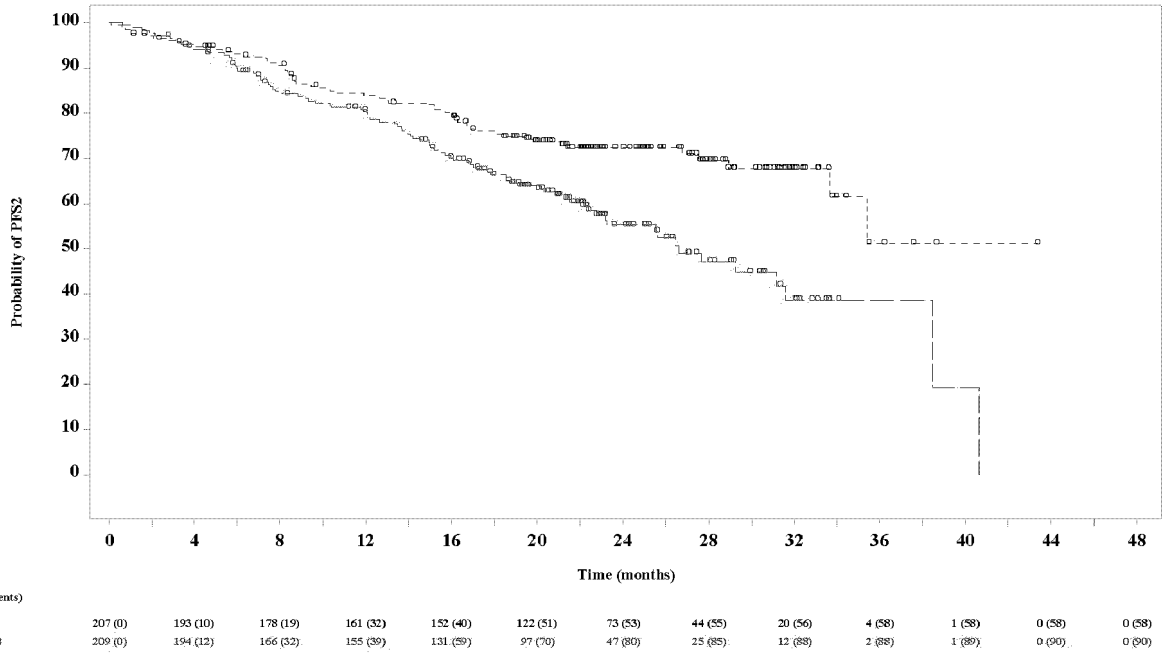
Fifty-eight subjects (28.0%) in the IDL + BR group and 90 subjects (43.1%) in the placebo + BR group reported a PFS2 event. The median (95% CI) time to PFS2 was not reached (33.7 months, NR) for subjects in the IDL + BR group and was 26.6 (22.8, 38.5) months for subjects in the placebo + BR group. The unadjusted HR (95% CI) was 0.57 (0.41, 0.79) and the p-value based on an unstratified log-rank test was 6.648×10^{-4}.

Table 4 GS-US-312-0115: Progression-Free Survival on Second-Line Therapy (ITT Analysis Set)

	IDL + BR (N = 207)	PI + BR (N = 209)
Number (%) of Subjects with Events	58 (28.0)	90 (43.1)
PD	11 (19.0)	32 (35.6)
Death	47 (81.0)	58 (64.4)
Number (%) of Subjects Censored	149 (72.0)	119 (56.9)
KM Estimate of PFS2 (Months)[a]		
Q1 (95% CI)	18.4 (15.2, 28.9)	14.1 (11.8, 16.9)
Median (95% CI)	NR (33.7, NR)	26.6 (22.8, 38.5)
Q3 (95% CI)	NR (NR, NR)	38.5 (38.5, 40.6)
Unadjusted HR (95% CI)[b]	0.57 (0.41, 0.79)	
P-value Unstratified Log-Rank Test	6.648×10^{-4}	

PFS2 = progression-free survival on second-line therapy
a PFS2 (months) = (start date of second subsequent post anti-cancer therapy, date of death] – date of randomization + 1) / 30.4375.
b HRs and 95% CIs were calculated using the Cox proportional hazards model without any adjustments.
Source: CHMP Table 7

Figure 3 GS-US-312-0115: Kaplan-Meier Curve of Progression-Free Survival on Second-Line Therapy (ITT Analysis Set)



PFS2 = progression-free survival on second-line therapy
Source: CHMP Figure 7

Co-Rapporteur

Additional reassurance regarding the overall benefit of IDL+BR could be obtained from the KM curve of PFS on second line therapy time to subsequent anti-cancer treatment analysis, showing a favourable HR of 0.57 for IDL+BR treatment vs BR alone. However, reliability of the data is questioned due to the high proportion of missing data as also discussed in response to efficacy RSI#3. **PFS2** data as reported appear non-reliable due to the very high event rates in terms of deaths (81% vs. 64%). Furthermore next-line therapy is reported as unknown in 30 to 40% of patients (vs. yes or no).

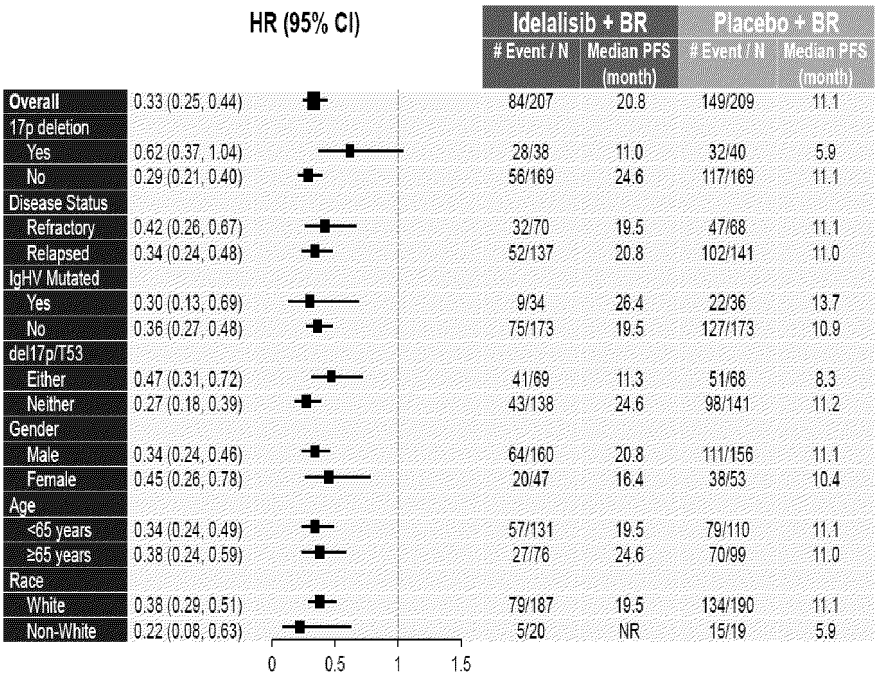
Issue partly resolved, remaining questions: Time to first and second next-line therapy should be reported based on the most recent study update. In the time to next-line analyses, deaths and missingness/lost to follow-up/unknown should be detailed (**both part of MO**). A sensitivity analysis for informative censoring should be performed, as reasons for censoring are not provided (72% in the IDL=BR arm versus 56.9%in the placebo + BR arm). Furthermore, the type of subsequent therapies is not provided and should be presented (both in one **OC**).

8. Please resubmit the forest plots including also medians (for the EPAR).

Applicant's Response

The requested forest plot for progression-free survival (PFS) based on a data cutoff date of 07 October 2015 is presented in Figure 4. The forest plot for OS based on a data cutoff date of 02 May 2016 is presented in Figure 4.

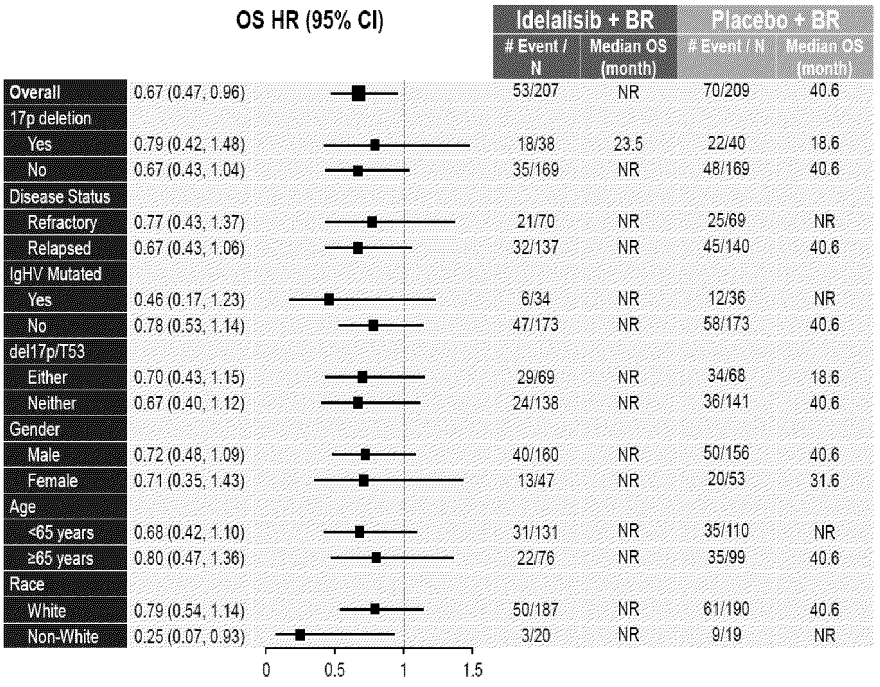
Forest Plot of Hazard Ratios for Progression-Free Survival by Subgroup, Data Cutoff of 07 October 2015 (ITT Analysis Set)



	HR (95% CI)	Idelalisib + BR # Event / N	Idelalisib + BR Median PFS (month)	Placebo + BR # Event / N	Placebo + BR Median PFS (month)
Overall	0.33 (0.25, 0.44)	84/207	20.8	149/209	11.1
17p deletion					
Yes	0.62 (0.37, 1.04)	28/38	11.0	32/40	5.9
No	0.29 (0.21, 0.40)	56/169	24.6	117/169	11.1
Disease Status					
Refractory	0.42 (0.26, 0.67)	32/70	19.5	47/68	11.1
Relapsed	0.34 (0.24, 0.48)	52/137	20.8	102/141	11.0
IgHV Mutated					
Yes	0.30 (0.13, 0.69)	9/34	26.4	22/36	13.7
No	0.36 (0.27, 0.48)	75/173	19.5	127/173	10.9
del17p/T53					
Either	0.47 (0.31, 0.72)	41/69	11.3	51/68	8.3
Neither	0.27 (0.18, 0.39)	43/138	24.6	98/141	11.2
Gender					
Male	0.34 (0.24, 0.46)	64/160	20.8	111/156	11.1
Female	0.45 (0.26, 0.78)	20/47	16.4	38/53	10.4
Age					
<65 years	0.34 (0.24, 0.49)	57/131	19.5	79/110	11.1
≥65 years	0.38 (0.24, 0.59)	27/76	24.6	70/99	11.0
Race					
White	0.38 (0.29, 0.51)	79/187	19.5	134/190	11.1
Non-White	0.22 (0.08, 0.63)	5/20	NR	15/19	5.9

Source: Data on file

Figure 4. Forest Plot of Hazard Ratios for Overall Survival by Subgroup, Data Cutoff of 02 May 2016 (ITT Analysis Set)



Source: Data on file

Rapporteur:
Requested data have been submitted, but preferably the latest survival cut-off should have been submitted **Not resolved**

9. If data on MRD were collected, please report.

Applicant's Response

Data on minimal residual disease (MRD) were not collected in this study.

Rapporteur:
There are no MRD data. **Resolved**

Question 10

The proposed indication is for patients "who have received at least one prior therapy". However, most included patients received 2 or more prior treatments, and the applicant is requested to present the proportion of patients that received only 1 prior therapy. (CoRapp)

Summary of MAH answer

Overall, 121 subjects (29.1%) received only 1 prior therapy regimen: 59 subjects (28.5%) in the IDL + BR group, and 62 subjects (29.7%) in the placebo + BR group. The number of prior regimens is presented in Table 5.

Table 5 GS-US-312-0115: Number of Prior Regimens (ITT Analysis Set)

	IDL + BR (N = 207)	PI + BR (N = 209)	Total (N = 416)
Number of Prior Regimens (n%)			
1	59 (28.5)	62 (29.7)	121 (29.1)
2	53 (25.6)	57 (27.3)	110 (26.4)
3	42 (20.3)	37 (17.7)	79 (19.0)
≥ 4	53 (25.6)	53 (25.4)	106 (25.5)

Source: CHMP Table 10

Rapporteur

The proportion of patients that received 1 prior therapy is provided as requested (n=121, 29.1%), and considered sufficient to consider the study population representative for the target population with the requested indication "patients who received at least one prior therapy".

Resolved

Question 11

In section 4.2 of the SmPC it is recommended to reduce the dose to 100 mg twice daily after a dose interruption. The applicant is asked to explain why a large percentage of patients that interrupted study treatment was rechallenged at a dose level of 150 mg BID, and to discuss the frequency of further dose modifications and treatment discontinuations after rechallenge. The median time to dose interruption, the number of dose interruptions per subject, and the duration of the dose interruption should be provided. The applicant should discuss whether the presented efficacy results are still representative for the 150 mg twice daily dose taking into account the percentage of expected doses to be taken and the number of days (or infusions) with treatment. (CoRapp)

Summary of MAH answer

The management of dose interruptions and rechallenges evolved as experience with idelalisib increased during clinical trials. In general, after a subject experienced an adverse event (AE) suspected to be related to IDL (based on investigator assessment), study drug could be withheld. Thereafter, depending on the AE and severity grade, study drug could be reinstituted at either the same dose level or at the reduced 100 mg twice daily dose (if the subject was previously treated at the 150 mg twice daily dose) at the investigator's discretion, using the protocol guidelines. For example, if a subject experienced Grade 3 or 4 fatigue, IDL was interrupted and resumed at the same level, whereas, if Grade 3 increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) was observed, IDL was withheld until abnormalities were ≤ Grade 1. Thereafter, if the subject had increased bilirubin < Grade 3, IDL was resumed at the same level whereas if bilirubin was ≥ Grade 3, IDL was resumed at a lower level. A summary of dose modifications is presented in Table 15.

Among subjects in the IDL + BR group, 119 subjects (57.5%) had an IDL dose modification. Most of these subjects (101 subjects, 84.9%) had dose modifications due to AEs. The most frequently reported AEs leading to IDL interruption in the IDL + BR group were diarrhea, increased ALT, and febrile neutropenia.

Among subjects in the placebo + BR group, 55 subjects (26.3%) had a placebo dose modification. Most of these subjects (46 subjects, 83.5%) had dose modifications due to AEs. The most frequently reported AEs leading to placebo interruption in the placebo + BR group were neutropenia, febrile neutropenia, granulocytopenia, and diarrhea.

In the majority of cases, investigators chose to rechallenge subjects at the same dose level after IDL dose interruption. This included subjects with dose interruptions unrelated to AEs. Two subjects (1.5%) had dose reductions without interruption (the dose for 1 subject was later re-escalated). Eighty-seven subjects (73.1%) with dose interruptions were rechallenged at 150 mg twice daily and 30 subjects (25.2%) were rechallenged at a lower dose. If the subject tolerated the lower dose of IDL for ≥ 4 weeks, the dose could be re-escalated to 150 mg twice daily, at the discretion of the investigator, particularly if further evaluation revealed that the AE leading to interruption was not study-drug related. Of the 30 subjects rechallenged at the lower dose (IDL 100 mg twice daily), 11 subjects (36.7%) met this criterion and were re-escalated to IDL 150 mg twice daily.

Most of the 117 subjects with dose interruptions in the IDL + BR group had either 1 interruption (58 subjects, 49.6%) or 2 interruptions (36 subjects, 30.8%). The median time to first IDL dose interruption was 2.1 months. The median duration of IDL interruptions (all interruption periods combined) was 1.1 months compared with the median duration of exposure to IDL of 18.2 months. Given the relatively short median duration of dose interruptions and the large proportion of subjects with interruptions who were rechallenged at IDL 150 mg twice daily or re-escalated to IDL 150 mg twice daily, the efficacy results are representative of the 150-mg twice daily dose.

Table 15 **GS-US-312-0115: Summary of Dose Modification of Idelalisib/Placebo (Safety Analysis Set)**

	IDL + BR (N = 207)	PI + BR (N = 209)
Subjects with Dose Modifications, n (%)	119 (57.5)	55 (26.3)
Modification due to AE	101 (48.8)	46 (22.0)
Modification due to Other	1 (0.5)	2 (1.0)
Modification due to AE and Other	17 (8.2)	7 (3.3)
Subjects with Dose Reductions without Interruption	2 (1.0)	1 (0.5)
Subjects with Dose Re-escalations	1 (0.5)	0
Subjects with Dose Interruptions[a]	117 (56.5)	54 (25.8)
Mean (StD)	1.8 (1.08)	1.4 (0.81)
Median	2.0	1.0
Q1, Q3	1.0, 2.0	1.0, 1.0
Min, Max	1.0, 7.0	1.0, 4.0
Number of Dose Interruptions, n (%)		
0	90 (43.5)	155 (74.2)
1	58 (28.0)	41 (19.6)
2	36 (17.4)	6 (2.9)
≥ 3	23 (11.1)	7 (3.3)
Time to First Dose Interruption (months)		
Mean (StD)	4.2 (5.45)	4.2 (3.63)
Median	2.1	2.8
Q1, Q3	1.1, 4.3	1.0, 6.0
Min, Max	0.1, 28.3	0.0, 13.1
Duration of Dose Interruptions (months)[b]		
N	117	54
Mean (StD)	1.5 (1.62)	0.9 (1.12)
Median	1.1	0.5
Q1, Q3	0.5, 1.7	0.3, 1.0
Min, Max	0.1, 12.4	0.1, 5.7
Subjects with Dose Rechallenged[c]	117 (54.5)	54 (25.8)
Subjects Rechallenged at 150 mg	87 (42.0)	40 (19.1)
Subjects Rechallenged at 100 mg	30 (14.5)	14 (6.7)
Subjects With Dose Re-escalation	11 (5.3)	4 (1.9)

	IDL + BR (N = 207)	Pl + BR (N = 209)
Duration of Exposure to IDL/Placebo (months)[d]		
N	207	208
Mean (StD)	16.1 (10.25)	11.4 (6.49)
Median	18.2	11.1
Q1, Q3	5.8, 24.0	5.8, 16.6
Min, Max	0, 43.4	0.5, 28.5

AE = adverse event
a Includes subjects with at least 1 dose interruption.
b Duration of dose interruption included all interruptions, not just the first interruption.
c First rechallenged dose after the first interruption was considered for this analysis.
d Duration of exposure (months) = (min [last IDL/Pl dosing date as captured on study drug completion electronic case report form (eCRF) page, data cutoff date] – first IDL/Pl dosing date + 1) / 30.4375.
Source: CHMP Table 11 and GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 5.12.1 and 5.12.2

Co-Rapporteur

It is acknowledged that the management of dose interruptions and rechallenges evolved as experience with idelalisib increased during clinical trials.

Eighty-seven patients (73.1%) with dose interruptions were rechallenged at 150 mg twice daily. Of the 30 patients (25.2%) rechallenged at the lower dose (IDL 100 mg twice daily), 11 subjects (36.7%) were re-escalated to IDL 150 mg twice daily. The median duration of IDL interruptions (all interruption periods combined) was 1.1 months compared with the median duration of exposure to IDL of 18.2 months. Given the relatively short median duration of dose interruptions and the large proportion of subjects with interruptions who were rechallenged at IDL 150 mg twice daily or re-escalated to IDL 150 mg twice daily, it is agreed with the applicant that efficacy results were representative of the 150-mg twice daily dose.

Issue resolved.

Question 12

The applicant is asked to present and discuss PFS KM curves for patients with or without 17p deletion and/or TP53 mutation. The applicant is furthermore asked to discuss the observed differences in PFS and OS results between the 17p deletion patient group and the 17p deletion and/or TP53 mutation patient group.

Summary of MAH answer

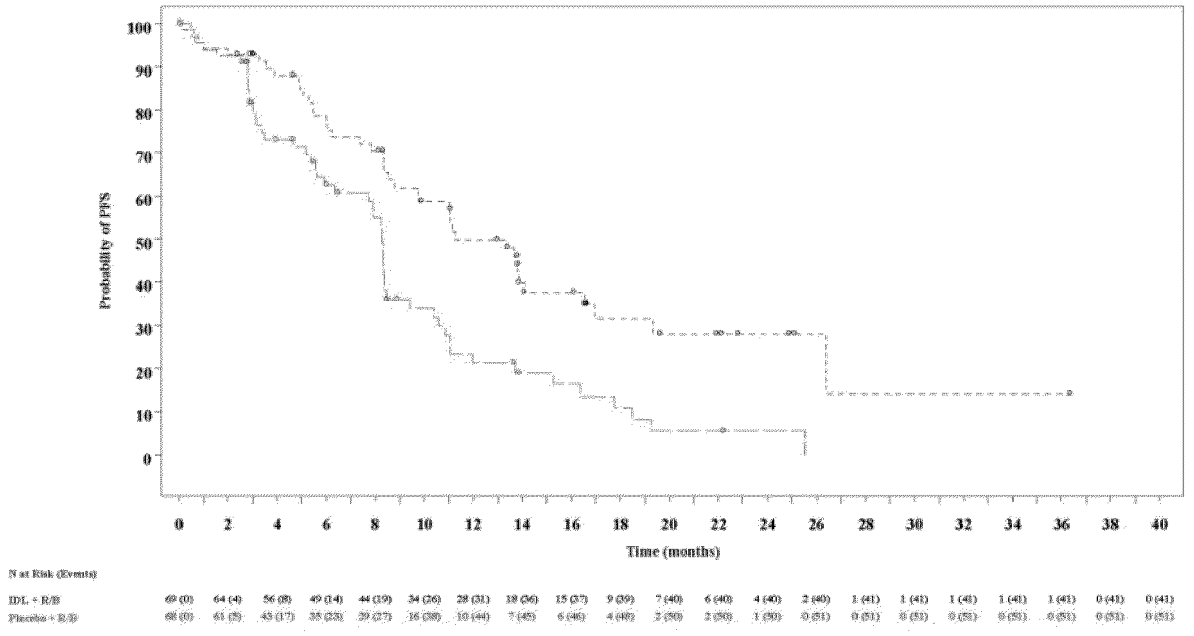
Progression-free survival, as assessed by the IRC based on the ITT Analysis Set are summarized in Table 6 by 17p deletion and/or TP53 mutation status (either vs neither); the KM plots are presented in Figure 5.

Table 6 GS-US-312-0115: Progression-Free Survival by IRC Assessment, Subjects with 17p Deletion and/or TP53 Mutation (Either) vs Subjects without 17p Deletion or TP53 Mutation (Neither) (ITT Analysis Set)

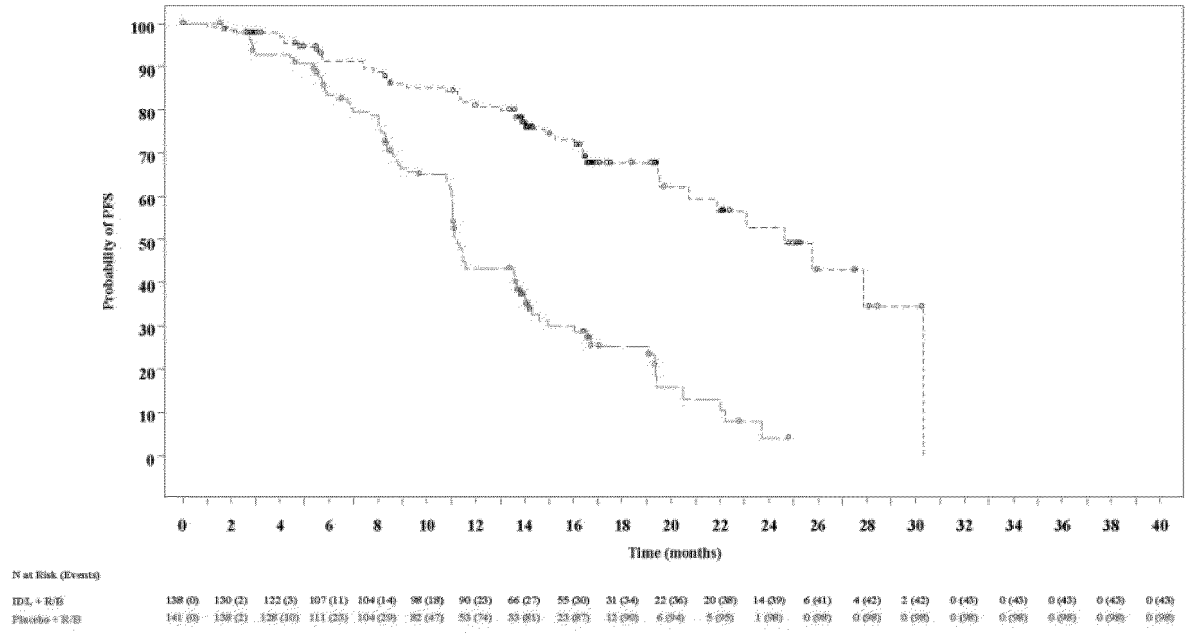
	Subjects with 17p Deletion and/or TP53 Mutation (Either)		Subjects without 17p Deletion or TP53 Mutation (Neither)	
	IDL + BR (N = 69)	PI + BR (N = 68)	IDL + BR (N = 138)	PI + BR (N = 141)
Number (%) of Subjects with Events	41 (59.4)	51 (75.0)	43 (31.2)	98 (69.5)
PD	30 (43.5)	42 (61.8)	30 (21.7)	88 (62.4)
Death	11 (15.9)	9 (13.2)	13 (9.4)	10 (7.1)
Number (%) of Subjects Censored	28 (40.6)	17 (25.0)	95 (68.8)	43 (30.5)
Ongoing	16 (23.2)	3 (4.4)	66 (47.8)	28 (19.9)
Discontinued Study	11 (15.9)	13 (19.1)	28 (20.3)	14 (9.9)
Received Another Antitumor Treatment	1 (1.4)	1 (1.5)	1 (0.7)	1 (0.7)
KM Estimate of PFS (Months)[a]				
Q1 (95% CI)	6.3 (4.9, 8.5)	3.4 (2.8, 5.6)	14.8 (11.4, 19.5)	8.1 (6.2, 8.8)
Median (95% CI)	11.3 (8.8, 16.6)	8.3 (5.9, 8.5)	24.6 (19.5, 30.3)	11.2 (11.1, 13.6)
Q3 (95% CI)	26.4 (16.6, NR)	11.1 (8.5, 17.8)	30.3 (27.9, 30.3)	19.1 (14.3, 20.5)
KM Estimate of PFS Rate (95% CI)				
At 24 weeks	78.3 (66.1, 86.6)	67.8 (54.6, 77.9)	93.7 (87.8, 96.8)	88.4 (81.8, 92.8)
At 48 weeks	56.9 (43.7, 68.1)	27.5 (16.3, 40.0)	84.3 (76.5, 89.7)	60.1 (51.2, 67.9)
Unadjusted HR (95% CI)[b]	0.47 (0.31, 0.72)		0.27 (0.18, 0.39)	

a PFS (months) = (minimum [date of PD, date of death] − date of randomization + 1) / 30.4375.
b HR and 95% CIs were calculated using the Cox proportional hazards model without any adjustment.
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 2.1.1.1 and 2.1.1.2

Figure 5 Kaplan-Meier Plots of Progression-Free Survival by IRC Assessment, Subjects with 17p Deletion and/or TP53 Mutation (Either) vs Subjects without 17p Deletion or TP53 Mutation (Neither) (ITT Analysis Set)



Subjects with 17p Deletion and/or TP53 Mutation (Either)
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Figure 1.1.1



Subjects without 17p Deletion or TP53 Mutation (Neither)
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Figure 1.1.2

Progression-free survival, as assessed by the IRC based on the ITT Analysis Set, for subjects with 17p deletion only and for subjects with 17p deletion and/or TP53 mutation is summarized in Table 7 and the KM plots are presented in Figure 6.

Among subjects with 17p deletion only, PFS following treatment with IDL + BR was superior to treatment with placebo + BR, with an unadjusted HR (95% CI) of 0.62 (0.37, 1.04). Among subjects with 17p deletion and/or TP53 mutation, PFS following treatment with IDL + BR was superior to treatment with placebo + BR, with an unadjusted HR (95% CI) of 0.47 (0.31, 0.72).

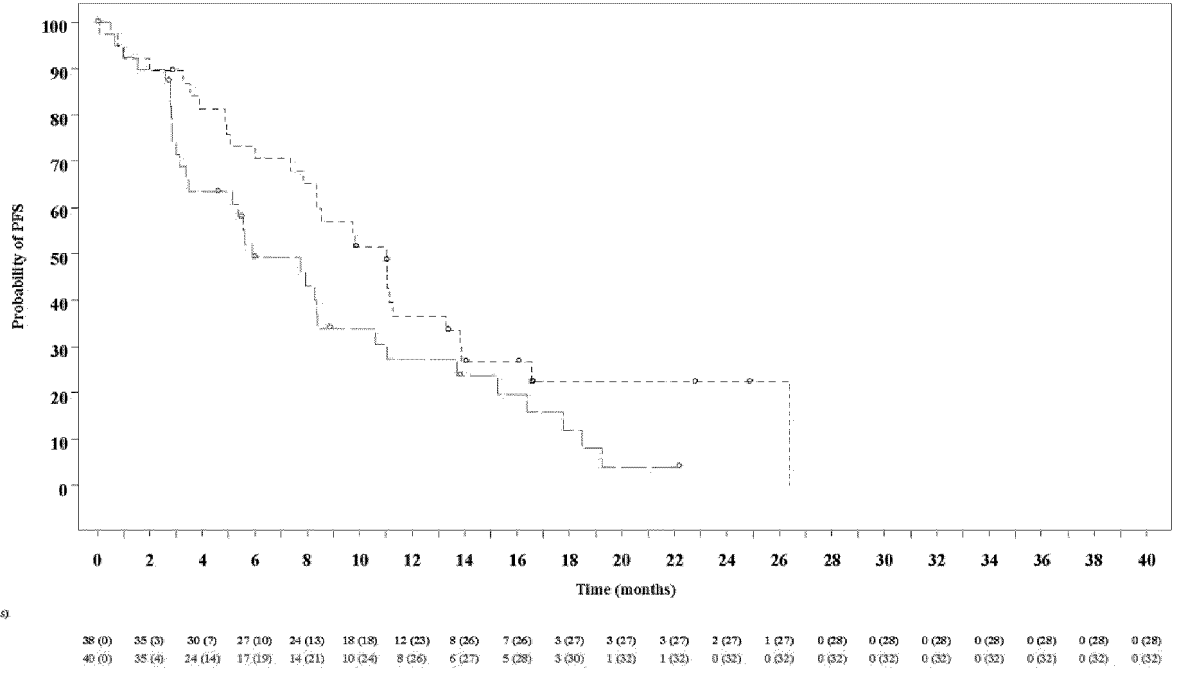
Among subjects treated with IDL + BR, the KM estimate of median PFS (95% CI) was 11.0 (7.9, 13.3) months for subjects with 17p deletion only, and 11.3 (8.8, 16.6) months for subjects with 17p deletion and/or TP53 mutation (Table 7). The KM estimate for median PFS was similar for subjects with 17p deletion and/or TP53 mutation compared with subjects with 17p deletion only.

Table 7 GS-US-312-0115: Progression-Free Survival by IRC Assessment (Subjects with 17p Deletion Only vs Subjects with 17p Deletion and/or TP53 Mutation) (ITT Analysis Set)

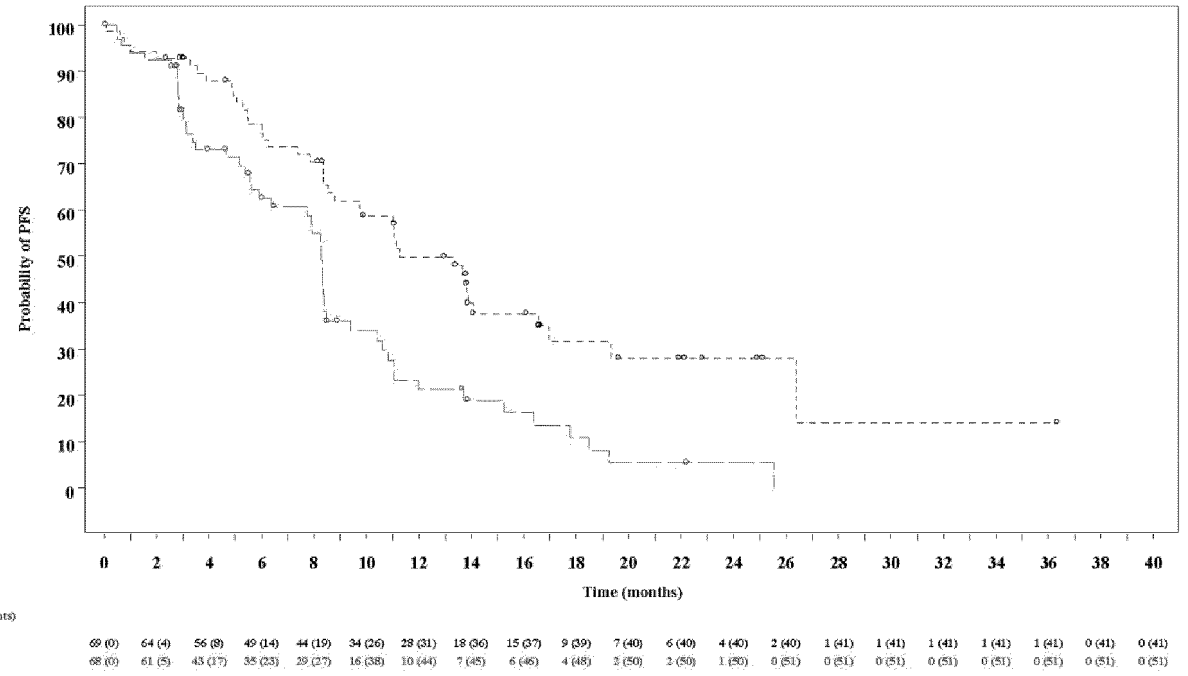
	Subjects with 17p Deletion Only		Subjects with 17p Deletion and/or TP53 Mutation	
	IDL + BR (N = 38)	PI + BR (N = 40)	IDL + BR (N = 69)	PI + BR (N = 68)
Number (%) of Subjects with Events	28 (73.7)	32 (80.0)	41 (59.4)	51 (75.0)
PD	20 (52.6)	25 (62.5)	30 (43.5)	42 (61.8)
Death	8 (21.1)	7 (17.5)	11 (15.9)	9 (13.2)
Number (%) of Subjects Censored	10 (26.3)	8 (20.0)	28 (40.6)	17 (25.0)
Ongoing	7 (18.4)	2 (5.0)	16 (23.2)	3 (4.4)
Discontinued Study	3 (7.9)	5 (12.5)	11 (15.9)	13 (19.1)
Received Another Antitumor Treatment	0	1 (2.5)	1 (1.4)	1 (1.5)
KM Estimate of PFS (Months)[a]				
Q1 (95% CI)	5.1 (2.0, 8.3)	2.9 (1.5, 5.2)	6.3 (4.9, 8.5)	3.4 (2.8, 5.6)
Median (95% CI)	11.0 (7.9, 13.3)	5.9 (3.4, 8.4)	11.3 (8.8, 16.6)	8.3 (5.9, 8.5)
Q3 (95% CI)	16.6 (11.1, 26.4)	13.7 (8.3, 18.5)	26.4 (16.6, NR)	11.1 (8.5, 17.8)
KM Estimate of PFS Rate (95% CI)				
At 24 weeks	73.2 (55.9, 84.6)	57.9 (40.7, 71.7)	78.3 (66.1, 86.6)	67.8 (54.6, 77.9)
At 48 weeks	48.7 (31.9, 63.5)	30.4 (16.1, 46.1)	56.9 (43.7, 68.1)	27.5 (16.3, 40.0)
Unadjusted HR (95% CI)[b]	0.62 (0.37, 1.04)		0.47 (0.31, 0.72)	

a PFS (months) = (minimum [date of PD, date of death] − date of randomization + 1) / 30.4375.
b HR and 95% CIs were calculated using the Cox proportional hazards model without any adjustment.
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 2.1.1.1, 2.1.1.2, and 2.1.1.5

Figure 6. Kaplan-Meier Plots of Progression-Free Survival by IRC Assessment, Subjects with 17p Deletion vs Subjects with 17p Deletion and/or TP53 Mutation (ITT Analysis Set)



Subjects with 17p Deletion Only
Source: GS-US-312-0115 Interim 1 CSR Section 15 Figure 1.1.5



Subjects with 17p Deletion and/or TP53 Mutation (Either)
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Figure 1.1.1

Overall survival, based on the ITT Analysis Set, for subjects with 17p deletion only and for subjects with 17p deletion and/or TP53 mutation is summarized in Table 8 and the KM plots are presented in Figure 7.

Among subjects with 17p deletion only, OS following treatment with IDL + BR was superior to OS following treatment with placebo + BR, with an unadjusted HR (95% CI) of 0.79 (0.42, 1.48). Among subjects with 17p deletion and/or TP53 mutation, OS following treatment with IDL + BR was superior to OS for subjects treated with placebo + BR, with an unadjusted HR (95% CI) of 0.70 (0.43, 1.15).

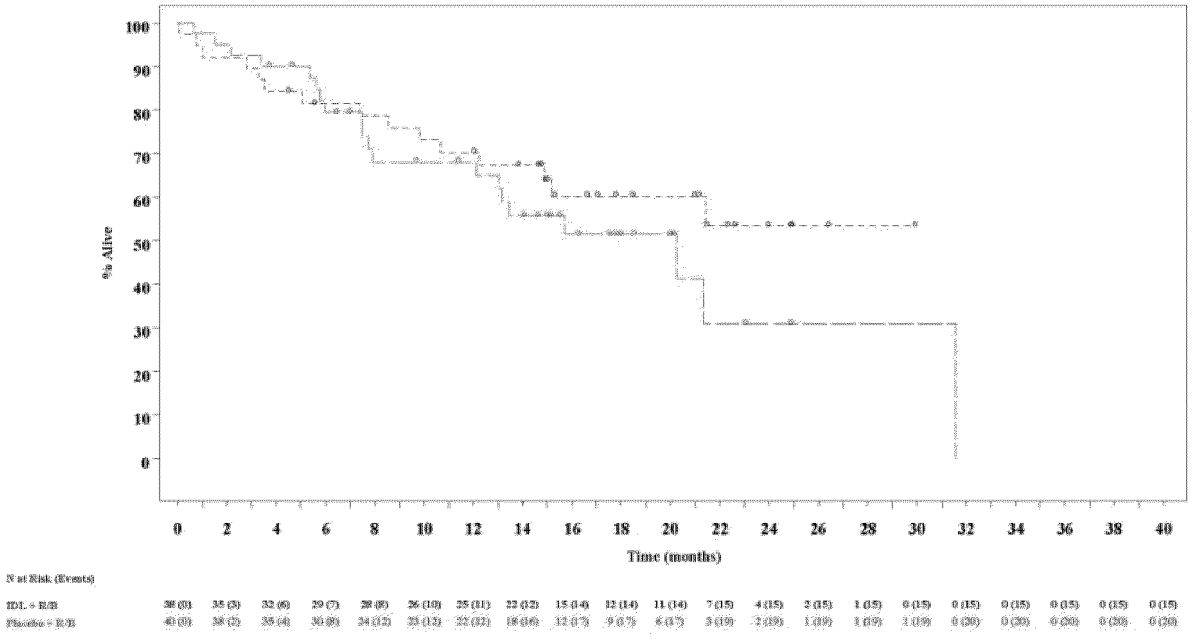
For subjects treated with IDL + BR, the KM estimate of median OS (95% CI) was 23.5 (12.2, not reached [NR]) months for subjects with 17p deletion only and was NR (18.4 months, NR) for subjects with 17p deletion and/or TP53 mutation (Table 8). The KM estimate for OS was longer for subjects with 17p deletion and/or TP53 mutation compared with subjects with 17p deletion only.

Table 8 GS-US-312-0115: Overall Survival by IRC Assessment, Subjects with 17p Deletion Only vs Subjects with 17p Deletion and/or TP53 Mutation (ITT Analysis Set)

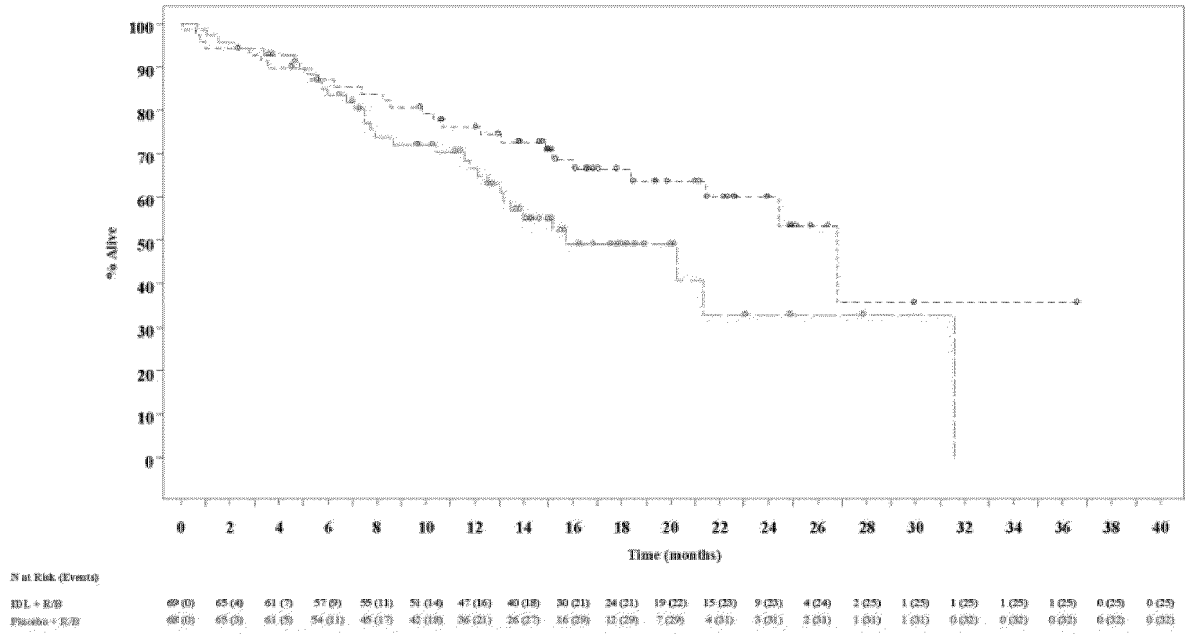
	Subjects with 17p Deletion Only		Subjects with 17p Deletion and/or TP53 Mutation	
	IDL + BR (N = 38)	PI + BR (N = 40)	IDL + BR (N = 69)	PI + BR (N = 68)
Number (%) of Subjects with Events	18 (47.4)	22 (55.0)	29 (42.0)	34 (50.0)
Death	18 (47.4)	22 (55.0)	29 (42.0)	34 (50.0)
Number (%) of Subjects Censored	20 (52.6)	18 (45.0)	40 (58.0)	34 (50.0)
Discontinued Study	16 (42.1)	16 (40.0)	28 (40.6)	31 (45.6)
Ongoing	4 (10.5)	2 (5.0)	12 (17.4)	3 (4.4)
KM Estimate of OS (Months)[a]				
Q1 (95% CI)	9.9 (2.8, 16.1)	7.5 (5.4, 13.2)	12.2 (6.3, 16.9)	7.9 (5.7, 12.6)
Median (95% CI)	23.5 (12.2, NR)	18.6 (12.1, 31.6)	NR (18.4, NR)	18.6 (13, NR)
Q3 (95% CI)	NR (NR, NR)	31.6 (NR, NR)	NR (NR, NR)	31.6 (31.6, NR)
Unadjusted HR (95% CI)[b]	0.79 (0.42, 1.48)		0.7 (0.43, 1.15)	

a OS (months) = (date of death − date of randomization + 1) / 30.4375.
b HR and 95% CI were calculated using the Cox proportional hazards model without any adjustments.
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 7.1.1, 7.1.2, and 7.1.5

Figure 7 Kaplan-Meier Plots of Overall Survival by IRC Assessment, Subjects with 17p Deletion Only vs Subjects with 17p Deletion and/or TP53 Mutation (ITT Analysis Set)



Subjects with 17p Deletion Only
Source: GS-US-312-0115 Interim 1 CSR Section 15 Figure 1.4.5



Subjects with 17p Deletion and/or TP53 Mutation (Either)
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Figure 1.4.1

Co-Rapporteur

The primary endpoint PFS showed a treatment benefit for IDL + BR in patients with only 17p deletion (HR 0.62) and in patients with 17p deletion and/or TP53 mutation (HR0.47). The requested KM curves were provided, and the KM estimates for median PFS were similar for patients with 17p deletion and/or TP53 mutation compared with subjects with 17p deletion only (~11 months).

OS following treatment with IDL + BR was superior in both 17p deletion only (HR 0.79) and 17p deletion and/or TP53 mutation (HR 0.70) groups. However, the KM estimate for OS was longer for subjects with 17p deletion and/or TP53 mutation (23.5 months) compared with subjects with 17p deletion only (18.4 months). KM curves of IDL+ BR and BR even crossed in 17p deletion patients in favour of the BR arm. It is however acknowledged that the study was underpowered to show statistically significant differences in OS subgroup analysis.

Issue resolved, but concerns regarding OS data are further discussed in OC 2.

Question 13

In 12.9% of placebo treated patients (vs. 0% in the IDL + BR treatment group) the reason for study discontinuation was study wide unblinding. It is not known why this occurred, and whether the blinding was sufficiently preserved throughout the study. The applicant is asked to elaborate.

Summary of response

Based on results from the prespecified interim analysis, the Independent Data Monitoring Committee (IDMC) recommended stopping the study for efficacy. Upon review of the data and following discussion with "regulatory agencies", Gilead did end the study early for efficacy. Treatment assignments were unblinded study-wide on 16 November 2015. At that time, subjects randomized to treatment with placebo appropriately discontinued receiving placebo and continued with study procedures per protocol.

Subject Disposition before unblinding data cut-off 07 October 2015 (ITT Analysis Set)

Subject Disposition	IDL + BR (N = 207) n (%)	Pl + BR (N = 209) n (%)	Total (N = 416) n (%)
Randomized	207 (100)	209 (100)	416 (100)
Treated	207 (100)	209 (100)	416 (100)
Treatment Ongoing	90 (43.5)	45 (21.5)	135 (32.5)
Met Primary Study Endpoint	34 (16.4)	100 (47.8)	134 (32.2)
PD	32 (15.5)	99 (47.4)	131 (31.5)
Death	2 (1.0)	1 (0.5)	3 (0.7)
Discontinued Treatment[b]	83 (40.1)	64 (30.6)	147 (35.3)
AE	56 (27.1)	28 (13.4)	84 (20.2)
Physician Decision	7 (3.4)	24 (11.5)	31 (7.5)
Withdrawal by Subject	12 (5.8)	8 (3.8)	20 (4.8)
Other	8 (3.9)	4 (1.9	

Subject Disposition after unblinding data cut-off 02 May 2016 (ITT Analysis Set)

Subject Disposition	IDL + BR (N = 207) n (%)	Pl + BR (N = 209) n (%)	Total (N = 416) n (%)
Randomized	207 (100)	209 (100)	416 (100)
Randomized but Not Treated With IDL/Pl	0	1 (0.5)	1 (0.2)
Treated with Any Drug[a]	207 (100)	209 (100)	416 (100)
Treatment Ongoing[b]	65 (31.4)	1 (0.5)	66 (15.9)
Met Primary Study Endpoint[c]	42 (20.3)	115 (55.0)	157 (37.7)
PD	40 (19.3)	114 (54.5)	154 (37.0)
Death	2 (1.0)	1 (0.5)	3 (0.7)
Discontinued Treatment[c]	100 (48.3)	92 (44.0)	192 (46.2)
AE	64 (30.9)	29 (13.9)	93 (22.4)
Physician Decision	9 (4.3)	24 (11.5)	33 (7.9)
Study-Wide Unblinding	0	27 (12.9)	27 (6.5)
Withdrawal by Subject	16 (7.7)	8 (3.8)	24 (5.8)
Other	11 (4.9)	4 (1.9)	9 (2.2)

a "Any drug" refers to any protocol-specified drug, ie, bendamustine, IDL, placebo, or rituximab.
b For 1 subject in the placebo + BR group (Subject [redacted]), treatment was listed as ongoing due to a data entry error; no subject in the placebo + BR group was continuing treatment at the data cutoff date of 02 May 2016.
c Reason for discontinuation was determined by the investigator.

Rapportuer:

The MAH has clarified. Note that AE led to study drug discontinuation in 31% of patients in the experimental arm vs. 14% in the control group (May 2016 cut-off).

The cross-over possibility was removed from the protocol in March 2016 (study wide unblinding November 2015) due to safety concerns (article 20). It is unclear how many patients crossed over after progression and after unblinding.

Resolved

Question 14

Disposition of patients has been presented several times by the applicant, with slightly different frequencies. The applicant is asked to clarify which data regarding the patient flow in study GS-US-312-0115 is correct. (CoRapp)

Summary of MAH answer

Based upon the recommendation of the IDMC and following review of the data and discussion with regulatory agencies, Gilead stopped the study early due to efficacy. Treatment assignments were unblinded study-wide on 16 November 2015. At that time, subjects randomized to treatment with placebo discontinued receiving placebo and continued with study procedures per protocol.

The primary analysis of data used a data cutoff date of 07 October 2015, just prior to unblinding on 16 November 2015. The presentations referred to in this response were correct, and differed slightly based on the data cut-off date used for the output. The Study GS-US-312-0115 Interim 1 CSR contains a discussion of the disposition of subjects using the primary analysis data cutoff of 07 October 2015, and presents tabular data from the data cutoff date for the Interim 1 CSR (after unblinding) of 02 May 2016.

Study GS-US-312-0115 Interim 1 CSR, Section 15.1, Table 5 2 summarized subject disposition data with respect to study treatment (IDL or placebo) at the time of the CSR data cutoff date (02 May 2016). Subject disposition data presented in the Study GS-US-312-0115 Interim 1 CSR Section 15.1, Table 5.1 summarized data with respect to continuation on study, whether or not subjects were still receiving treatment.

Co-Rapporteur

The differences in disposition data have been clarified by the applicant.

Issue resolved.

Question 15

The applicant stated that 75% of PFS events had occurred at the time of the interim analysis, which exceeds the planned frequency of 66%. Based on the number of events (presented in Table 9 (Primary Endpoint: PFS by IRC Assessment, 07 October 2015 (ITT), the actual frequency of PFS events seemed to be lower (56%). The applicant is asked to clarify. (CoRapp)

Summary of MAH answer

In the Interim 1 CSR, the following statement was based on the total number of planned PFS events at the final PFS analysis, ie, 66% of 260 the total number of planned PFS events. Based on results from

this prespecified interim analysis (data cutoff date of 15 June 2015), by which time 23 more events had actually occurred, or 75% of PFS events had occurred), the IDMC recommended stopping the study for efficacy."

The discussed frequency for PFS events of 56%, Study GS-US-312-0115 Interim 1 CSR, Section 15.1, Table 2.1.1, is based on a data cutoff date of 07 October 2015, and represents the reported numbers based on the total number of subjects in the ITT Analysis Set (N = 416).

Co-Rapporteur

The differences in planned and actual frequency of PFS events have been clarified.

Issue resolved.

Question 16

The applicant stated that an increase of 10 points in Karnofsky Perfomance Status (KPS) has been observed for the IDL + BR treated patients. This would be similar to the 10 points increase observed with IDL + R alone. However, based on the median scores provided in Table 15 (baseline 90, best change from baseline/highest value 90), an improvement of 0 points is expected, as is the case for the placebo + BR treated patients. The applicant is asked to clarify. (CoRapp)

Summary of MAH answer

Karnofsky Performance Status (KPS) has a discrete 11-point measurement scale (0, 10, 20, … 100). Median best change from baseline was 10 points for IDL + BR group, and 0 points for the placebo + BR group. As shown in Table 9, a greater proportion of subjects in the IDL + BR group than the placebo + BR group shifted to higher KPS values. This shift was highest between scores of 90 and 100, from 18.4% to 45.9% for subjects in the IDL + BR group, compared with from 22.5% to 37.8% for subjects in the placebo + BR group.

To determine "Change from Baseline," the best change from baseline score was first derived for each subject, and then the median of those changes was calculated. This is different from directly comparing the 2 medians at baseline and at best postbaseline, which sometimes does not reflect the true change, especially when the scores are discrete. An illustrating example involving only 3 subjects would be as follows: scores at baseline of 80, 90, and 90 with median = 90 points, and scores at best postbaseline of 90, 90, and 100, also with median = 90 points; however, the median change from baseline would be 10 points.

Table 9 GS-US-312-0115: Baseline and Highest Postbaseline Karnofsky Performance Status Values

	IDL + BR (N = 207)		Placebo + BR (N = 209)	
KPS Score	**Baseline**	**Highest Postbaseline Value**	**Baseline**	**Highest Postbaseline Value**
50	0	0	1 (0.5)	1 (0.5)
60	5 (2.4)	3 (1.4)	6 (2.9)	1 (0.5)
70	22 (10.6)	4 (1.9)	18 (8.6)	7 (3.3)

80	61 (29.5)	26 (12.6)	58 (27.8)	31 (14.8)
90	81 (39.1)	75 (36.2)	79 (37.8)	87 (41.6)
100	38 (18.4)	95 (45.9)	47 (22.5)	79 (37.8)

KPS = Karnofsky Performance Status
Source: CHMP Table 16

Co-Rapporteur

The applicant clarified that the 10 point improvement in KPS values was based on the best change from baseline score. This was first determined for each patient, and then the median of those changes was calculated. This is different from directly comparing the 2 medians at baseline and at best postbaseline, which sometimes does not reflect the true change.

Issue resolved.

Question 17

Efficacy results in study GS-US-312-0115 have been presented for patients <65 and ≥65 years of age, safety results have been presented for *3 age* groups: (< 65 (N = 131), 65 to < 75 (N = 60), and 75 to < 85 (N = 16) years of age). Since the median age of the intended target population is relatively high, the applicant is asked to present efficacy results for these 3 age groups as well.

Summary of MAH answer

The requested additional posthoc analyses of efficacy results for subjects < 65, 65 to < 75, and ≥ 75 years of age were generated. The subgroup of subjects ≥ 75 years of age treated with IDL + BR contained only 16 subjects; therefore, the efficacy results for that subgroup should be interpreted with caution.

Progression-Free Survival

Progression-free-survival by age subgroup (< 65, 65 to < 75, and ≥ 75 years of age), as assessed by the IRC based on the ITT Analysis Set, is summarized in Table 10. PFS following treatment with IDL + BR was superior to PFS following treatment with placebo + BR in all age subgroups, with unadjusted HRs (95% CIs) of 0.34 (0.24, 0.49) for subjects < 65 years of age, 0.41 (0.25, 0.69) for subjects 65 to < 75 years of age, and 0.26 (0.09, 0.75) for subjects ≥ 75 years of age.

Among subjects < 65 years of age, 57 subjects (43.5%) in the IDL + BR group and 79 subjects (71.8%) in the placebo + BR group had a PFS event. The KM estimate of median PFS (95% CI) was 19.5 (16.1, 25.8) months for subjects in the IDL + BR group and 11.1 (8.8, 11.3) months for subjects in the placebo + BR group.

Among subjects 65 to < 75 years of age, 22 subjects (36.7%) in the IDL + BR group and 56 subjects (70.9%) in the placebo + BR group reported a PFS event. The KM estimate of median PFS (95% CI) was 24.6 (11.9, 30.3) months for subjects in the IDL + BR group and 11.0 (8.4, 14.1) months for subjects in the placebo + BR group.

Among subjects ≥ 75 years of age, 5 subjects (31.3%) in the IDL + BR group and 14 subjects (70.0%) in the placebo + BR group reported a PFS event. The KM estimate of median PFS (95% CI) was not reached (15.2 months, NR) for subjects in the IDL + BR group and was 11.1 (5.6, 13.7) months for subjects in the placebo + BR group.

Table 10 GS-US-312-0115: Progression-Free Survival by Age Group (< 65, 65 to < 75, and ≥ 75 Years of Age) by IRC Assessment (ITT Analysis Set)

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
Number (%) of Subjects with Events	57 (43.5)	79 (71.8)	22 (36.7)	56 (70.9)	5 (31.3)	14 (70.0)
PD	42 (32.1)	73 (66.4)	15 (25.0)	48 (60.8)	3 (18.8)	9 (45.0)
Death	15 (11.5)	6 (5.5)	7 (11.7)	8 (10.1)	2 (12.5)	5 (25.0)
Number (%) of Subjects Censored	74 (56.5)	31 (28.2)	38 (63.3)	23 (29.1)	11 (68.8)	6 (30.0)
Ongoing	51 (38.9)	16 (14.5)	24 (40.0)	13 (16.5)	7 (43.8)	2 (10.0)
Discontinued Study	22 (16.8)	14 (12.7)	13 (21.7)	9 (11.4)	4 (25.0)	4 (20.0)
Received Another Antitumor Treatment	1 (0.8)	1 (0.9)	1 (1.7)	1 (1.3)	0	0
KM Estimate of PFS (Months)[a]						
Q1 (95% CI)	11.1 (8.3, 13.8)	6.9 (5.4, 8.3)	9.2 (4.9, 13.3)	8.0 (5.4, 8.3)	15.2 (0.8, NR)	5.6 (1.5, 10.8)
Median (95% CI)	19.5 (16.1, 25.8)	11.1 (8.8, 11.3)	24.6 (11.9, 30.3)	11.0 (8.4, 14.1)	NR (15.2, NR)	11.1 (5.6, 13.7)
Q3 (95% CI)	27.9 (25.8, NR)	15.2 (11.6, 19.3)	30.3 (24.6, 30.3)	17.8 (14.3, 22.2)	NR (16.5, NR)	13.7 (11.1, NR)
KM Estimate of PFS Rate (95% CI)						
At 24 weeks	90.1 (83.3, 94.3)	80.9 (72, 87.2)	87.2 (74.9, 93.7)	84.5 (74.3, 90.9)	80.4 (50.6, 93.2)	78.8 (52.8, 91.5)
At 48 weeks	76.1 (67.3, 82.9)	51.6 (41.2, 61)	70.6 (55.9, 81.2)	49.4 (37.4, 60.3)	80.4 (50.6, 93.2)	50.0 (25.7, 70.3)
Unadjusted HR (95% CI)[b]	0.34 (0.24, 0.49)		0.41 (0.25, 0.69)		0.26 (0.09, 0.75)	

a PFS (months) = (minimum (date of PD, date of death) − date of randomization + 1)/30.4375.
b Hazard ratio and 95% CIs were calculated using the Cox proportional hazards model without any adjustments.
Source: CHMP Tables 17.1.1 and 17.1.2, and GS-US-312-0115 Interim 1 CSR Section 15.1 Table 2.1.1.11

Overall Response Rate

A summary of overall response rate (ORR) by age subgroup is presented in Table 11. ORR for subjects treated with IDL + BR was superior to that for subjects treated with placebo + BR in each age subgroup.

Among subjects < 65 years of age, the ORR (95% CI) (classified as complete response (CR), complete response with incomplete marrow recovery (CRi), or PR with minimal duration of 12 weeks) for the ITT Analysis Set was 73.3% (64.8%, 80.6%) for the IDL + BR group and 41.8% (32.5%, 51.6%) for the placebo + BR group. The odds ratio (95% CI) for ORR was 3.82 (2.22, 6.56), which favored IDL + BR over placebo + BR.

Among subjects 65 to < 75 years of age, the ORR (95% CI) was 63.3% (49.9%, 75.4%) for the IDL + BR group and 50.6% (39.1%, 62.1%) for the placebo + BR group. The odds ratio (95% CI) for ORR was 1.68 (0.85, 3.34), which favored IDL + BR over placebo + BR.

Among subjects ≥ 75 years of age, the ORR (95% CI) was 68.8% (41.3%, 89.0%) for the IDL + BR group and 40.0% (19.1%, 63.9%) for the placebo + BR group. The odds ratio (95% CI) for ORR was 3.3 (0.83, 13.18), which favored IDL + BR over placebo + BR.

Table 11 GS-US-312-0115: Overall Response Rate by Age Group (< 65, 65 to < 75, and ≥ 75 Years of Age) by IRC Assessment (ITT Analysis Set)

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
Best Overall Response, n (%)						
CR	2 (1.5)	0	1 (1.7)	0	0	0
CRi	0	1 (0.9)	0	0	0	0
PR	94 (71.8)	45 (40.9)	37 (61.7)	40 (50.6)	11 (68.8)	8 (40.0)
SD	27 (20.6)	48 (43.6)	16 (26.7)	28 (35.4)	4 (25.0)	9 (45.0)
PD	0	12 (10.9)	1 (1.7)	5 (6.3)	0	2 (10.0)
NE	8 (6.1)	4 (3.6)	5 (8.3)	6 (7.6)	1 (6.3)	1 (5.0)
ORR[a] n (%)	96 (73.3)	46 (41.8)	38 (63.3)	40 (50.6)	11 (68.8)	8 (40.0)
95% CI[b]	64.8, 80.6	32.5, 51.6	49.9, 75.4	39.1, 62.1	41.3, 89.0	19.1, 63.9
Odds Ratio for ORR[c]	3.82		1.68		3.30	
95% CI	2.22, 6.56		0.85, 3.34		0.83, 13.18	

CR = complete response; CRi = complete response with incomplete marrow recovery; ORR = overall response rate
a ORR was the percentage of subjects that had best overall response of CR, CRi, or PR.
b 95% CI for ORR was based on the exact method.
c Odds ratio and 95% CI were calculated without any adjustment.
Subjects with CR, CRi, or PR who maintained the response for at least 12 weeks were defined to have confirmed response; otherwise, response status was categorized as SD.
Source: CHMP Tables 17.2.1 and 17.2.2, and GS-US-312-0115 Interim 1 CSR Section 15.1 Table 2.2.1.11

Lymph Node Response Rate

A summary of the lymph node response (LNR) rate by age subgroup is presented in Table 12.

Among subjects < 65 years of age, the LNR rate (95% CI) was 96.7% (91.8%, 99.1%) for the IDL + BR group and 56.2% (46.2%, 65.9%) for the placebo + BR group. The odds ratio (95% CI) for the LNR rate was 23.00 (7.90, 66.95), which favored IDL + BR over placebo + BR.

Among subjects 65 to < 75 years of age, the LNR rate (95% CI) was 98.2% (90.3%, 100%) for the IDL + BR group and 69.9% (58.0%, 80.1%) for the placebo + BR group. The odds ratio (95% CI) for the LNR rate was 23.29 (3.03, 179.19), which favored IDL + BR over placebo + BR.

Among subjects ≥ 75 years of age, the LNR rate (95% CI) was 93.3% (68.1%, 99.8%) for the IDL + BR group and 52.6% (28.9%, 75.6%) for the placebo + BR group. The odds ratio (95% CI) for the LNR rate was 12.60 (1.37, 115.97), which favored IDL + BR over placebo + BR.

Table 12 GS-US-312-0115: Lymph Node Response Rate by Age Group (< 65, 65 to < 75, and ≥ 75 Years of Age) by IRC Assessment (ITT Analysis Set)

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
LNR Rate[a] n/N (%)	118/122 (96.7)	59/105 (56.2)	54/55 (98.2)	51/73 (69.9)	14/15 (93.3)	10/19 (52.6)
95% CI[b]	91.8, 99.1	46.2, 65.9	90.3, 100	58.0, 80.1	68.1, 99.8	28.9, 75.6
Odds Ratio[c]	23.00		23.29		12.60	
95% CI for Odds Ratio	7.90, 66.95		3.03, 179.19		1.37, 115.97	

LNR = lymph node response; SPD = sum of the products of greatest perpendicular diameters
a LNR rate was defined as the percentage of subjects who achieved a ≥ 50% decrease from baseline in the SPD of index lymph nodes.
b 95% CI for response rate was based on the exact method.
c Odds ratio and 95% CI were calculated without any adjustment.
The analysis only includes subjects in the ITT Analysis Set who had both baseline and at least 1 evaluable post-baseline SPD.
Source: CHMP Tables 17.3.1 and 17.3.2, and GS-US-312-0115 Interim 1 CSR Section 15.1 Table 2.4.1.11

Overall Survival

A summary of OS by age subgroup is presented in Table 13.

Among subjects < 65 years of age, 54 subjects died on study: 24 subjects (18.3%) in the IDL + BR group and 30 subjects (27.3%) in the placebo + BR group. The unadjusted HR (95% CI) for OS was 0.59 (0.34, 1.01) which favored IDL + BR over placebo + BR.

Among subjects 65 to < 75 years of age, 44 subjects died on study: 19 subjects (31.7%) in the IDL + BR group and 25 subjects (31.6%) in the placebo + BR group. The unadjusted HR (95% CI) for OS was 1.03 (0.57, 1.89) which did not favor IDL + BR over placebo + BR.

Among subjects ≥ 75 years of age, 13 subjects died on study: 3 subjects (18.8%) in the IDL + BR group and 10 subjects (50.0%) in the placebo + BR group. The unadjusted HR (95% CI) for OS was 0.30 (0.08, 1.09) which favored IDL + BR over placebo + BR.

Table 13 GS-US-312-0115: Overall Survival by Age Group (< 65, 65 to < 75, and ≥ 75 Years of Age) (ITT Analysis Set)

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
Number (%) of Subjects with Events (Deaths)	24 (18.3)	30 (27.3)	19 (31.7)	25 (31.6)	3 (18.8)	10 (50.0)
Number (%) of Subjects Censored	107 (81.7)	80 (72.7)	41 (68.3)	54 (68.4)	13 (81.3)	10 (50.0)
Discontinued Study	45 (34.4)	55 (50.0)	23 (38.3)	45 (57.0)	9 (56.3)	9 (45.0)
Ongoing	62 (47.3)	25 (22.7)	18 (30.0)	9 (11.4)	4 (25.0)	1 (5.0)
KM Estimate of OS (Months)[a]						

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
Q1 (95% CI)	NR (16.0, NR)	15.0 (12.1, 20.3)	16.7 (8.7, 27.5)	17.2 (8.7, 40.6)	NR (0.8, NR)	12.7 (1.5, 20.8)
Median (95% CI)	NR (NR, NR)	31.6 (20.3, NR)	NR (26.8, NR)	40.6 (NR, NR)	NR (NR, NR)	26.6 (11.8, NR)
Q3 (95% CI)	NR (NR, NR)	NR (31.6, NR)	NR (NR, NR)	40.6 (NR, NR)	NR (NR, NR)	NR (26.6, NR)
Unadjusted HR (95% CI)[b]	0.59 (0.34, 1.01)		1.03 (0.57,1.89)		0.30 (0.08, 1.09)	

a OS (months) = (date of death – date of randomization + 1) / 30.4375
b HR and 95% CI were calculated using the Cox proportional hazards model without any adjustments.
Source: CHMP Tables 17.4.1 and 17.4.2, and GS-US-312-0115 Interim 1 CSR Section 15.1 Table 2.5.1.11

Duration of Response

A summary of duration of response (DOR) is presented in Table 14.

Among subjects < 65 years of age, the KM estimate of median DOR (95% CI) was 22.8 (14.9, 24.8) months for subjects in the IDL + BR group and 8.7 (8.3, 15.7) months for subjects in the placebo + BR group.

Among subjects 65 to < 75 years of age, the KM estimate of median DOR (95% CI) was 27.2 (16.6, 27.2) months for subjects in the IDL + BR group and 11.7 (10.8, 18.5) months for subjects in the placebo + BR group.

Among subjects ≥ 75 years of age, the KM estimate of median DOR (95% CI) was not reached (13.4 months, NR) for subjects in the IDL + BR group and 8.6 (5.2, NR) months for subjects in the placebo + BR group.

Table 14 GS-US-312-0115: Duration of Response by Age Group (< 65, 65 to < 75, and ≥ 75 Years of Age) by IRC Assessment (ITT Analysis Set)

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
Number (%) of Subjects with CR, CRi, or PR	96 (73.3)	46 (41.8)	38 (63.3)	40 (50.6)	11 (68.8)	8 (40.0)
Number (%) of Subjects with Events	35 (36.5)	28 (60.9)	10 (26.3)	24 (60.0)	1 (9.1)	6 (75.0)
PD	29 (30.2)	28 (60.9)	8 (21.1)	24 (60.0)	1 (9.1)	5 (62.5)
Death	6 (6.3)	0	2 (5.3)	0	0	1 (12.5)
Number (%) of Subjects Censored	61 (63.5)	18 (39.1)	28 (73.7)	16 (40.0)	10 (90.9)	2 (25.0)
Ongoing	51 (53.1)	14 (30.4)	24 (63.2)	12 (30.0)	7 (63.6)	2 (25.0)
Discontinued Study	10 (10.4)	3 (6.5)	3 (7.9)	4 (10.0)	3 (27.3)	0
Received Another Antitumor Treatment	0	1 (2.2)	1 (2.6)	0	0	0

	< 65 Years of Age		65 to < 75 Years of Age		≥ 75 Years of Age	
	IDL + BR (N = 131)	PI + BR (N = 110)	IDL + BR (N = 60)	PI + BR (N = 79)	IDL + BR (N = 16)	PI + BR (N = 20)
KM Estimate of DOR (Months)[a]						
Q1 (95% CI)	11.0 (9.0, 13.8)	5.8 (5.6, 8.3)	16.6 (7.4, 27.2)	8.3 (5.6, 11.3)	NR (13.4, NR)	8.1 (5.2, 8.6)
Median (95% CI)	22.8 (14.9, 24.8)	8.7 (8.3, 15.7)	27.2 (16.6, 27.2)	11.7 (10.8, 18.5)	NR (13.4, NR)	8.6 (5.2, NR)
Q3 (95% CI)	24.8 (22.8, NR)	16.6 (13.6, NR)	27.2 (21.6, 27.2)	19.1 (16.2, 20.9)	NR (13.4, NR)	NR (8.2, NR)

DOR = duration of response
a DOR (months) = (minimum [date of PD, date of death] – date of first documented CR, CRi, or PR + 1) / 30.4375.
Analysis only included subjects who achieved CR, CRi, or PR.
Subjects with CR, CRi, or PR who maintained the response for at least 12 weeks were defined to have confirmed response; otherwise, response status was categorized as SD.
Source: CHMP Tables 17.5.1 and 17.5.2, and GS-US-312-0115 Interim 1 CSR Section 15.1 Table 2.6.1.11

Co-Rapporteur

Efficacy results have been provided for the three age groups (< 65 (N = 131 in the IDL + BR arm), 65 to < 75 (N = 60), and 75 to < 85 (N = 16) years of age. Benefit has been observed with IDL + BR over BR alone in all three age groups for the primary endpoint PFS, and secondary endpoints ORR, lymph node response rate, duration of response. Median OS was not reached in the three age groups, but the HR suggest that patients in the age group 65 to <75 have no OS benefit from the addition of IDL to BR treatment (HR 1.03). It is however acknowledged that the study was underpowered to show statistically significant differences in OS subgroup analysis.

Issue resolved, but concerns regarding OS data are further discussed in OC 2.

Question 18

The per protocol analysis set was added to the pivotal study protocol as an amendment in Dec 2012. However, results of the pre-specified sensitivity analyses with the PP analysis set for the primary and secondary endpoints were not presented, and the applicant is asked to submit these data and discuss whether results were comparable to the ITT analysis set. (CoRapp)

Summary of MAH answer

Primary Endpoint: Progression-Free Survival

Progression-free survival results were comparable between the ITT and Per Protocol (PP) Analysis Sets. In both analysis sets, IDL + BR was superior to placebo + BR. In the ITT Analysis Set, the adjusted HR (95% CI) was 0.33 (0.25, 0.44) with a 2-sided p-value < 0.0001 based on a stratified log-rank test. In the PP Analysis Set, the adjusted HR (95% CI) was 0.34 (0.26, 0.45) with a 2-sided p-value < 0.0001 based on a stratified log-rank test (Table 15).

Among subjects in the ITT Analysis Set, 84 subjects (40.6%) in the IDL + BR group and 149 subjects (71.3%) in the placebo + BR group reported PFS events. The median (95% CI) PFS was 20.8 (16.6, 26.4) months for subjects in the IDL + BR group and 11.1 (8.9, 11.1) months for subjects in the placebo + BR group.

Among subjects in the PP Analysis Set, a total of 84 subjects (41.6%) in the IDL + BR group and 143 subjects (71.1%) in the placebo + BR group reported a PFS event. The KM estimate of median PFS (95% CI) was 19.5 (16.5, 25.8) months for subjects in the IDL + BR group and 11.1 (8.8, 11.1) months for subjects in the placebo + BR group.

Table 15 GS-US-312-0115: Progression-Free Survival by IRC Assessment (ITT and PP Analysis Sets)

	ITT Analysis Set		PP Analysis Set	
	IDL + BR (N = 207)	PI + BR (N = 209)	IDL + BR (N = 202)	PI + BR (N = 201)
Number (%) of Subjects with Events	84 (40.6)	149 (71.3)	84 (41.6)	143 (71.1)
PD	60 (29.0)	130 (62.2)	60 (29.7)	125 (62.2)
Death	24 (11.6)	19 (9.1)	24 (11.9)	18 (9.0)
Number (%) of Subjects Censored	123 (59.4)	60 (28.7)	118 (58.4)	58 (28.9)
Ongoing	82 (39.6)	31 (14.8)	81 (40.1)	31 (15.4)
Discontinued Study	39 (18.8)	27 (12.9)	35 (17.3)	25 (12.4)
Received Another Antitumor Treatment	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
KM Estimate of PFS (Months)[a]				
Q1 (95% CI)	11 (8.3, 13.6)	6.9 (5.6, 8.1)	11 (8.3, 13.3)	6.9 (5.6, 8.1)
Median (95% CI)	20.8 (16.6, 26.4)	11.1 (8.9, 11.1)	19.5 (16.5, 25.8)	11.1 (8.8, 11.1)
Q3 (95% CI)	30.3 (26.4, NR)	16.1 (14.0, 19.3)	30.3 (26.4, NR)	16.6 (14.0, 19.3)
KM Estimate of PFS Rate (95% CI)				
At 24 weeks	88.5 (83.0, 92.3)	82.1 (76.0, 86.7)	88.3 (82.7, 92.1)	82.5 (76.3, 87.1)
At 48 weeks	75.0 (68.0, 80.6)	50.5 (43.2, 57.5)	74.5 (67.5, 80.3)	50.4 (42.8, 57.4)
Adjusted HR (95% CI)[b]	0.33 (0.25, 0.44)		0.34 (0.26, 0.45)	
P-value[c]	6.540×10^{-16}		5.917×10^{-15}	

The PP Analysis Set included all subjects in the ITT Analysis Set who met the PP criteria defined in the Statistical Analysis Plan (SAP), with treatment group designated according to the actual treatment received.

a PFS (months) = (minimum [date of PD, date of death] − date of randomization + 1) / 30.4375.

b HR and 95% CIs were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors in electronic data capture (EDC) (17p deletion/TP53 mutation, IGHV mutation status, and disease status).

c P-value was from the stratified log-rank test, adjusted for randomization stratification factors.

Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 2.1.1 and 2.1.2

Secondary Endpoint: Overall Survival

Per the study protocol Section 9.3.1.2, the PP Analysis Set was used in sensitivity analyses of the following primary and secondary efficacy endpoints: PFS, ORR, LNR rate, and CR rate. Therefore, no sensitivity analysis of OS was conducted for the PP Analysis Set.

Secondary Endpoint: Overall Response Rate

Overall response rate results were comparable between the analysis sets. The odds ratio for ORR favored IDL + BR over placebo + BR for the ITT and PP Analysis Sets (p-value < 0.0001 for both analysis sets) (Table 16).

The ORR (95% CI) (classified as CR, CRi, or PR with minimal duration of 12 weeks) for the ITT Analysis Set was 70.0% (63.3%, 76.2%) for the IDL + BR group and 45.0% (38.1%, 52.0%) for the placebo + BR group. The odds ratio (95% CI) for the ORR was 3.09 (2.02, 4.72), which favored IDL + BR compared with placebo + BR (p-value < 0.0001).

The ORR (95% CI) for the PP Analysis Set was 70.3% (63.5%, 76.5%) for the IDL + BR group and 45.8% (38.7%, 52.9%) for the placebo + BR group. The odds ratio (95% CI) for the ORR was 3.05 (1.98, 4.70), which favored IDL + BR compared with placebo + BR (p-value < 0.0001).

Table 16 GS-US-312-0115: Overall Response Rate by IRC Assessment (ITT and PP Analysis Sets)

	ITT Analysis Set		PP Analysis Set	
	IDL + BR (N = 207)	PI + BR (N = 209)	IDL + BR (N = 202)	PI + BR (N = 201)
Best Overall Response, n (%)				
CR	3 (1.4)	0	3 (1.5)	0
CRi	0	1 (0.5)	0	1 (0.5)
PR	142 (68.6)	93 (44.5)	139 (68.8)	91 (45.3)
SD	47 (22.7)	85 (40.7)	45 (22.3)	82 (40.8)
PD	1 (0.5)	19 (9.1)	1 (0.5)	18 (9.0)
NE	14 (6.8)	11 (5.3)	14 (6.9)	9 (4.5)
ORR (n%)[a]	145 (70.0)	94 (45.0)	142 (70.3)	92 (45.8)
95% CI[b]	63.3, 76.2	38.1, 52.0	63.5, 76.5	38.7, 52.9
Odds Ratio for Overall Response[c]	3.09		3.05	
95% CI for Odds Ratio	2.02, 4.72		1.98, 4.70	
P-value	1.054×10^{-7}		2.323×10^{-7}	

PP = Per Protocol Analysis Set
The PP Analysis Set included all subjects in the ITT Analysis Set who met the PP criteria defined in the SAP, with treatment group designated according to the actual treatment received.
Subjects with CR, CRi, or PR who maintained the response for at least 12 weeks were defined to have confirmed response. Otherwise, response status was categorized as SD.
a ORR was the percentage of subjects who had best overall response of CR, CRi, or PR.
b 95% CI for ORR was based on the exact method.
c Odds ratio, 95% CI, and p-value were calculated from the Cochran-Mantel-Haenszel (CMH) Chi-square test stratified by stratification factors in EDC (17p deletion/TP53 mutation, IGHV mutation status, and disease status).
Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 2.2.1 and 2.2.2

Secondary Endpoint: Lymph Node Response Rate

Lymph node response rate results were comparable between the analysis sets. The odds ratio for LNR rate favored IDL + BR over placebo + BR for the ITT and PP Analysis Sets (p-value < 0.0001 for both analysis sets) (Table 17).

The LNR rate (95% CI) for the ITT Analysis Set was 96.9% (93.3%, 98.8%) for the IDL + BR group and 60.9% (53.7%, 67.8%) for the placebo + BR group. The stratified odds ratio (95% CI) for the LNR rate was 28.72 (10.48, 78.72), favoring IDL + BR over placebo + BR (p-value < 0.0001).

The LNR rate (95% CI) for the PP Analysis Set was 96.8% (93.1%, 98.8%) for the IDL + BR group and 61.8% (54.5%, 68.7%) for the placebo + BR group. The stratified odds ratio (95% CI) for the LNR rate was 26.62 (9.74, 72.72), favoring IDL + BR over placebo + BR (p-value < 0.0001).

Table 17 GS-US-312-0115: Lymph Node Response Rate by IRC Assessment (ITT and PP Analysis Sets)

	ITT Analysis Set		PP Analysis Set	
	IDL + BR (N = 207)	PI + BR (N = 209)	IDL + BR (N = 202)	PI + BR (N = 201)
LNR Rate[a], n/N (%)	186/192 (96.9)	120/197 (60.9)	181/187 (96.8)	118/191 (61.8)
95% CI for LNR Rate[b]	93.3, 98.8	53.7, 67.8	93.1, 98.8	54.5, 68.7
Odds Ratio[c]	28.72		26.62	
95% CI for Odds Ratio	10.48, 78.72		9.74, 72.72	
P-value	1.681×10^{-19}		1.548×10^{-18}	

Analysis only included subjects in the ITT Analysis Set or PP Analysis Set who had both baseline and at least 1 evaluable postbaseline SPD.

a LNR rate was defined as the percentage of subjects who achieved a ≥ 50% decrease from baseline in the SPD of index lymph nodes. (Denominator is the number of subjects with baseline and at least 1 postbaseline measurement.)

b 95% CI for response rate was based on the exact method.

c Odds ratio, 95% CI, and p-value was calculated from the CMH Chi-square test stratified by stratification factors in EDC (17p deletion/TP53 mutation, IGHV mutation status, and disease status).

Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 2.4.1 and 2.4.2

Secondary Endpoint: Complete Response Rate

Complete response rate results were comparable between the analysis sets (Table 18). Of the 3 documented CRs on study, all were observed in the IDL + BR group (rate of 1.4% for the ITT Analysis Set and 1.5% for the PP Analysis Set).

Table 18 GS-US-312-0115: Complete Response Rate by IRC Assessment (ITT and PP Analysis Sets)

	ITT Analysis Set		PP Analysis Set	
	IDL + BR (N = 207)	PI + BR (N = 209)	IDL + BR (N = 202)	PI + BR (N = 201)
Complete Response, n (%)	3 (1.4)	0	3 (1.5)	0
95% CI[a]	0.3, 4.2	0, 1.7	0.3, 4.3	0, 1.8
P-value[b]	1.223×10^{-1}		2.481×10^{-1}	

a 95% CI for response rate was based on the exact method.

b P-value from Fisher's exact test.

Source: GS-US-312-0115 Interim 1 CSR Section 15.1 Tables 2.3.1 and 2.3.4

Co-Rapporteur

It is reassuring that the PP analysis of the primary endpoint PFS and secondary endpoints ORR, lymph node response rate, CR rate were all in favour of IDL + BR and supported the primary analysis in the ITT population.

No PP analysis for OS has been performed, as this was not pre-specified in the study protocol, which is accepted.

Issue resolved.

Question 19

In the study report of the pivotal study, the applicant stated that a separate biomarker analysis plan will be prepared to detail pharmacodynamics and biomarker analyses. Biomarker results could however not be found in the dossier and the applicant is requested to submit information regarding disease-associated biomarkers, and to discuss potential mechanisms of resistance to IDL, based on published and in-house data, eg, in relation to PI3K mutation status. (CoRapp)

Summary of MAH answer

While IDL therapy in CLL is efficacious, progressive disease after response occurs and has been observed in a subset of subjects on IDL treatment indicating that escape mechanisms can develop; however, the molecular basis for relapse or progressive disease in CLL subjects treated with IDL has not been characterized. In order to explore progressive disease-associated biomarkers, whole-exome sequencing (WES) on matched samples (peripheral blood mononuclear cells) at baseline and time of CLL progression was conducted in subjects enrolled in the following Phase 3 clinical trials: Study GS-US-312-0116, Study GS-US-312-0117, and Study GS-US-312-0119. Study PC-312-2018 Amendment 1 has been previously submitted and reviewed by CHMP (EMEA/H/C/003843/II/0025).

To date, 13 high quality subject samples from Studies GS-US-312-0116, GS-US-312-0117 and GS-US-312-0119 meeting the established sample criteria have been evaluated to understand mechanisms of IDL resistance in patients with CLL (PC-312-2018 Amendment 1). This analysis showed that there are no coding mutations within this subject set which would reveal a common mutational mechanism of IDL resistance, either a mutation in the drug binding site (so called "gateway mutation") or consistent mutations in any other pathway reflective of a common escape pathway/mechanism. If a common (> 20% frequency) relapse-associated mutation mechanism existed, there would only be a ≤ 5% chance of not observing this in even 1 of the 13 tested sample set.

To date, we have used whole exome sequencing (WES) to evaluate a total of 33 CLL subject samples: 13 subject samples met established sample selection criteria (PC-312-2018 Amendment 1) and 20 subject samples did not meet established sample selection criteria. The 33 subject samples were analyzed for the presence of any mutations in PI3Kδ, including the IDL binding region, and no mutations in PI3Kδ were identified (95% exact confidence interval for the prevalence of such mutation is: 0–11%). The current sample size of 33 is sufficiently large to allow a high chance (> 80% probability) of observing at least 1 subject with an IDL-mediated mutation in the PI3Kδ binding pocket even if this resistance mechanism is as rare as 5% frequency. While we cannot rule out the existence of a PI3Kδ mutation in a very small subset of subjects, such a gateway mutation does not exist in the current sample set of subjects with progressive disease on IDL. We thus conclude that a gateway mutation (a common mechanism of resistance with ibrutinib, found in approximately 80% of patients with progressive disease {Maddocks 2015, Woyach 2014}) is not expected to be a major resistance mechanism with IDL.

Given these results, profiling additional samples from Study GS-US-312-0115 is highly unlikely to add to our current knowledge of IDL-mediated mechanisms of resistance.

Co-Rapporteur

As discussed in question 20, the results above indicate that mutations of PI3Kδ are not considered to be a likely "resistance candidate".

Issue resolved.

Question 20.

PI3K mutations have been reported in a number of malignancies (Chaloub Ann Rev Pathol 2009). Please discuss if this is a concern in the treatment with IDL that would justify assessing PI3K status in patients with resistance to IDL.

Response

Study PC-312-2018 was conducted to evaluate mechanisms of resistance as a postauthorization measure for IDL in the European Union (EU). In this study, subjects with CLL from three Phase 3 clinical trials (Study GS-US-312-0116, Study GS-US-312-0117, and Study GS-US-312-0119) who progressed while on IDL treatment were evaluated.

Whole exome sequencing was used to evaluate a total of 33 CLL subject samples. The samples were analyzed for the presence of any mutations of PI3Kδ, including the IDL-binding region, and no mutations were identified (95% exact CI for the prevalence of such mutation: 0 to 11%). The sample size of 33 subjects was sufficiently large to allow a high chance (> 80% probability) of observing at least 1 subject with an IDL-mediated mutation in the PI3Kδ binding pocket, even if this resistance mechanism was as rare as 5% frequency. While the existence of a PI3Kδ mutation in a very small subset of subjects could not be ruled out, such a gateway mutation did not exist in the current sample set of subjects with progressive disease on IDL. A gateway mutation (a common mechanism of resistance with ibrutinib, found in approximately 80% of patients with progressive disease {Maddocks 2015, Woyach 2014}) is thus not expected to be a major resistance mechanism with IDL.

No mechanistic explanations for the development of resistance to treatment with IDL have been identified from clinical studies. Further investigation of this topic in current B-cell malignancy studies is not planned.

Rapporteur

Based on available data, mutations of PI3Kδ is not considered to be a likely "resistance candidate". This appears acceptable. Further studies aiming at defining mechanisms of resistance are not planned. At this stage, this is accepted.

Resolved

Question 21.

Is there a difference in baseline characteristics in the IDL + BR arm between patients with events of PFS ≤ 6 months, > 6 months and ≤ 18 months, and > 18 months? To contextualise, similar data may be reported for the PI + BR arm.

Summary of response

Demographics and baseline disease characteristics were similar between subjects in the IDL + BR group at each time-to-PFS-event category (≤ 6 months, > 6 months, ≤ 18 months, and > 18 months).

The exception was the KPS. In the IDL + BR group, subjects with better KPS (≥ 80%) were more likely to have events-to-PFS that occurred later (at > 18 months).

Characteristic	Events of PFS ≤ 6 Months			Events of PFS > 6 Months			Events of PFS ≤ 18 Months			Events of PFS > 18 Months		
	IDL+BR (N=25)	Pl+BR (N=46)	Total (N=71)	IDL+BR (N=59)	Pl+BR (N=103)	Total (N=162)	IDL+BR (N=73)	Pl+BR (N=138)	Total (N=211)	IDL+BR (N=11)	Pl+BR (N=11)	Total (N=22)
KPS, n (%)												
40	0	0	0	0	0	0	0	0	0	0	0	0
50	0	1 (2.2)	1 (1.4)	0	0	0	0	1 (0.7)	1 (0.5)	0	0	0
60	0	2 (4.3)	2 (2.8)	2 (3.4)	2 (1.9)	4 (2.5)	2 (2.7)	4 (2.9)	6 (2.8)	0	0	0
70	7 (28.0)	9 (19.6)	16 (22.5)	7 (11.9)	2 (1.9)	9 (5.6)	14 (19.2)	11 (8.0)	25 (11.8)	0	0	0
80	8 (32.0)	12 (26.1)	20 (28.2)	16 (27.1)	35 (34.0)	51 (31.5)	18 (24.7)	46 (33.3)	64 (30.3)	6 (54.5)	1 (9.1)	7 (31.8)
90	10 (40.0)	14 (30.4)	24 (33.8)	20 (33.9)	39 (37.9)	59 (36.4)	28 (38.4)	49 (35.5)	77 (36.5)	2 (18.2)	4 (36.4)	6 (27.3)
100	0	8 (17.4)	8 (11.3)	14 (23.7)	25 (24.3)	39 (24.1)	11 (15.1)	27 (19.6)	38 (18.0)	3 (27.3)	6 (54.5)	9 (40.9)

BMI = body mass index;
a. Age (years) = (date of randomization – date of birth + 1)/365.25
b. BMI (kg/m^2) = weight/height^2

No consistent differences in disease history were observed between time-to-PFS events categories.

Subjects in the IDL + BR group with a shorter time since completion of the last prior regimen had earlier PFS events. There were no other consistent differences between time-to-PFS event categories according to prior therapy.

	Events of PFS ≤ 6 months			Events of PFS > 6 months			Events of PFS ≤ 18 months			Events of PFS > 18 months		
	IDL+BR (N=25)	Pl+BR (N=46)	Total (N=71)	IDL+BR (N=59)	Pl+BR (N=103)	Total (N=162)	IDL+BR (N=73)	Pl+BR (N=138)	Total (N=211)	IDL+BR (N=11)	Pl+BR (N=11)	Total (N=22)
Median Time Since Completion of Last Prior Regimen, Months (Q1, Q3)[b]	11.4 (3.4, 19.0)	13.3 (7.5, 22.0)	12.6 (4.8, 21.3)	17.8 (5.1, 26.0)	14.7 (7.0, 27.4)	15.0 (5.6, 27.3)	14.0 (4.6, 22.3)	13.4 (6.4, 26.6)	13.5 (5.4, 24.9)	17.9 (4.4, 30.4)	25.5 (13.9, 33.7)	25.1 (10.8, 30.4)

Subjects with either a 17p deletion and/or Tp53 mutation treated with IDL + BR were more likely to experience early events of PFS, 14 subjects (56%) experienced events of PFS ≤ 6 months, while 2 subjects (18.2%) experienced events of PFS > 18 months.

Raporteur:

The rather comprehensive data set presented by the MAH (not shown), provide little evidence of value for the proper clinical use of idelalisib.

Resolved

Question 23 (22 according to applicant)

The applicant is asked to present results of the objective health resource utilization associated with the addition of IDL to BR, as these results could not be found. (CoRapp)

Summary of MAH answer

Health resource utilization was not directly measured. However, the EuroQol 5 Dimension (EQ-5D) was converted into a single utility index by applying the United States (US) preference-weighted index. This analysis was performed for a tertiary pharmacoeconomics endpoint assessing change in health status, which was defined as the change from basesline in overall health and single-item dimension scores as assessed using the EQ-5D utility measure.

Heath status information was obtained with the EQ-5D, which is a self-administered, generic, indirect utility measure {The EuroQol Group 1990}. The EQ-5D consists of a visual analogue scale on which subjects are asked to rate their current overall health status and 5 single-item dimensions which ask subjects to rate their health in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each of the 5 items patients must choose between 3 levels of difficulty in accomplishing tasks in that dimension. The dimension scores are used to generate a health utility score that can be incorporated into analyses of cost effectiveness or used as a quantitative measure of health outcome as judged by the individual respondents. The EQ-5D has been successfully used in the evaluation of patients with B-cell and other cancers {Doorduijn 2005, Witzens-Harig 2009, Yang 2010}.

A summary of the actual values and change from baseline at 4-week intervals for the first 12 weeks and at 6-month intervals thereafter for the EQ-5D Questionnaire Utility Index is provided in Table 19.

The EQ-5D utility index results were similar between the IDL + BR and the placebo + BR treatment groups. Compared to baseline, at Week 12 the mean overall utility decreased by 0.01 in the IDL + BR treatment group and 0.02 in the placebo + BR treatment group.

Table 19 GS-US-312-0115: Summary of EQ-5D Questionnaire Utility Index, Actual Values and Change from Baseline (ITT Analysis Set)

	IDL + BR (N = 207)		Placebo + BR (N = 209)	
	Actual	Change from Baseline	Actual	Change from Baseline
Baseline				
N	197	—	195	—
Mean (StD)	0.78 (0.217)	—	0.78 (0.228)	—
Median	0.80	—	0.81	—
Q1, Q3	0.73, 1.00	—	0.73, 1.00	—
Week 4				
N	187	182	192	181
Mean (StD)	0.80 (0.219)	0.02 (0.213)	0.77 (0.233)	-0.01 (0.198)
Median	0.85	0.00	0.81	0.00
Q1, Q3	0.69, 1.00	-0.07, 0.12	0.69, 1.00	-0.07, 0.00
Week 8				
N	176	169	188	176
Mean (StD)	0.79 (0.233)	0.00 (0.225)	0.79 (0.223)	0.01 (0.215)
Median	0.81	0.00	0.81	0.00
Q1, Q3	0.69, 1.00	-0.11, 0.12	0.73, 1.00	-0.05, 0.09
Week 12				
N	173	168	187	175
Mean (StD)	0.77 (0.254)	-0.01 (0.240)	0.76 (0.241)	-0.02 (0.213)
Median	0.81	0.00	0.81	0.00
Q1, Q3	0.69, 1.00	-0.11, 0.11	0.69, 1.00	-0.12, 0.04
Week 24				
N	154	149	150	141
Mean (StD)	0.80 (0.245)	0.01 (0.211)	0.78 (0.216)	-0.02 (0.227)
Median	0.85	0.00	0.80	0.00
Q1, Q3	0.71, 1.00	-0.04, 0.12	0.69, 1.00	-0.11, 0.05
Week 48				
N	128	123	104	98
Mean (StD)	0.83 (0.167)	0.03 (0.184)	0.80 (0.236)	0.02 (0.242)
Median	0.85	0.00	0.85	0.00
Q1, Q3	0.73, 1.00	-0.07, 0.12	0.73, 1.00	-0.07, 0.12
Week 72				
N	77	75	50	47
Mean (StD)	0.81 (0.231)	0.02 (0.236)	0.76 (0.281)	0.01 (0.335)
Median	0.85	0.00	0.80	0.00
Q1, Q3	0.73, 1.00	-0.10, 0.15	0.71, 1.00	-0.10, 0.19

	IDL + BR (N = 207)		Placebo + BR (N = 209)	
	Actual	**Change from Baseline**	**Actual**	**Change from Baseline**
Week 96				
N	33	33	14	13
Mean (StD)	0.79 (0.270)	-0.04 (0.216)	0.77 (0.306)	-0.01 (0.219)
Median	0.85	0.00	0.84	0.00
Q1, Q3	0.73, 1.00	-0.02, 0.05	0.71, 1.00	-0.12, 0.19
Week 120				
N	9	9	2	2
Mean (StD)	0.82 (0.154)	0.01 (0.187)	0.91 (0.132)	0.03 (0.038)
Median	0.85	0.00	0.91	0.03
Q1, Q3	0.69, 1.00	-0.11, 0.16	0.81, 1.00	0.00, 0.05
Week 144				
N	1	1	0	0
Mean (StD)	0.22	-0.63	—	—
Median	0.22	-0.63	—	—
Q1, Q3	0.22, 0.22	-0.63, -0.63	—	—

Source: GS-US-312-0115 Interim CSR Section 15.1 Table 2.12.3.3

Co-Rapporteur

Health resource utilization was not directly measured, but the EQ-5D was converted into a single utility index, measuring the change from baseline in overall health and single-item dimension scores. No differences in EQ-5D utility index results were observed between the IDL + BR and the placebo + BR treatment groups.

Issue resolved.

24. Please provide details as regards adherence to PJP and CMV prophylaxis.

Applicant's Response

A summary of subjects who experienced PJP during the study by PJP prophylaxis status was provided in the Study GS-US-312-0115 Interim 1 CSR Section 15 Table 8.3.

However, please note that on 25 March 2016, safety information and protocol guidelines for toxicity management were updated for consistency across IDL studies. These changes included mandated prophylaxis for PJP and mandated CMV surveillance. Because the requirements for PJP prophylaxis and CMV surveillance were not in place until GS-US-312-0115 Protocol Amendment 7, complete data regarding adherence to PJP prophylaxis and CMV surveillance were not collected for the entire duration of the study.

Rapporteur

Interpretable data are not available.

Resolved in the sense not further pursued.

Question 25.

Adverse reactions led to the stopping of all first-line studies. Please compare adverse events of special interest per 2 months period IDL + BR vs. BR in studies 0015 and 0023. Please also discuss whether there is a "true" increase in add-on toxicity related to line of therapy and if so if there are underlying mechanisms making this plausible.

Summary of response

Discontinuations due to AEs were almost twice as frequent over the first month and between Months 1 and 3 in the IDL + BR regimen of the front-line study (GS-US-312-0123) compared with the same regimens in the relapsed study population (Study GS-US-312-0115), indicating poorer tolerability of IDL + BR in the front-line setting. In both studies, there were more infectious SAEs overall in the IDL + BR regimen than in the placebo + BR regimen (40.1% vs 23.4% in the relapsed population and 30.8% vs 9.1% in the front-line population). However, the differences between the regimens in the front-line study was much greater than in the relapsed study due to the relatively low percentage of infectious SAEs in the front-line population receiving placebo + BR (9.1%).

Similarly, during the first month on study there were more deaths overall in the IDL + BR regimen than in the placebo + BR regimen. In the relapsed CLL study, the slight imbalance over 1 month was reversed between Months 1 and 3 and at time points thereafter, while the more significant imbalance in early deaths in the front-line CLL subjects remained. The absence of early deaths in the comparator arm of the front-line study is notable. The early deaths in the front-line study were almost entirely due to infectious AEs.

Adverse events of interest (AEIs) for IDL include events observed in previous studies with IDL as well as disease-related events associated with CLL. AEIs for IDL include bowel perforation of any grade, CMV infection of any grade, diarrhea/colitis ≥ Grade 3, febrile neutropenia ≥ Grade 3, infection ≥ Grade 3, PJP of any grade, pneumonitis of any grade, PML of any grade, and rash per Gilead MST ≥ Grade 3. No events of PML were reported during Study GS-US-312-0115.

The incidence and prevalence of AEIs for Study GS-US-312-0115 and Study GS-US-312-0123 are presented by 12-week interval in Table 44. Twelve-week intervals, rather than 2-month intervals, are provided herein to align with data provided in the CSRs.

The incidence and prevalence of ≥ Grade 3 diarrhea/colitis appears similar between the front-line and relapsed populations through Week 60, and thereafter appears higher in the relapsed population. The incidence and prevalence of ≥ Grade 3 febrile neutropenia appears similar between the front-line and relapsed populations through Week 48, and thereafter appears higher in the relapsed population. The incidence and prevalence of ≥ Grade 3 infections appeared higher in the front-line population for the first 12 weeks, and thereafter appeared higher in the relapsed population. The incidence and prevalence of ≥ Grade 3 rash per MST appears higher throughout the study in the front-line population.

The idelalisib development program experience to date does not support a by-line, overall increased add-on toxicity. The underlying mechanism for the increased early infectious events and associated fatalities seen in the idelalisib front-line CLL studies does not appear attributable to a single identified factor (eg severe neutropenia, decreased CD4+ counts, con-committant bendamustine administration), but is more likely due to heightened immunomodulatory effects experienced by some patients with a treatment-naïve immune system.

Rapporteur

The MAHs conclusions (yellow above) are supportive on a descriptive level and are in line with PRAC conclusions.

Resolved

Question 26.

In the protocol of study GS-US-312-0115 it was stated (in the section of dose modifications) that tumour lysis syndrome (TLS) had occurred in 5% of subjects treated with idelalisib in combination with bendamustine or bendamustine rituximab. In the safety summary and in the interim CSR of study GS-US-312-0115 no cases of TLS have been reported. The applicant is requested to clarify.

Applicant's Response

Study GS-US-312-0115 Protocol Amendment 9 included the following statement in the Premedications section (Section 5.3.2): In the absence of concomitant cytotoxic administration, tumor lysis syndrome is uncommon with either IDL or rituximab. Tumor lysis syndrome has occurred in ~5% of patients when IDL had been combined with bendamustine or bendamustine/rituximab. Investigators may wish to institute prophylaxis and monitoring for tumor lysis syndrome according to local practices.

In the integrated safety analysis of studies with IDL m2.7.4 (CLL sNDA ID+BR Jan 2017), tumor lysis syndrome was reported for the following:

- 11.1% of subjects treated with IDL + B
- 3.4% of subjects treated with IDL + BR
- 2.1% of subjects treated with IDL + R

Rapporteur:

The approximations are accepted.

Resolved

Clinical Safety Aspects

Question 27
It has not been reported whether cases of overdose in study GS-US-312-0115 have occurred. If so, narratives should be provided.

Applicant's Response

Overall, 6 subjects had dosing errors of study drug: 4 subjects randomized to treatment with IDL + BR and 2 subjects randomized to treatment with placebo + BR. There were 5 cases of overdosing and 1 case of underdosing. Narratives for the 6 dosing errors are as follows:

- Subject [redacted] (IDL + BR): Beginning 02 July 2014, the subject took 2 study drug tablets twice daily (for 300 mg IDL twice daily) rather than 1 tablet twice daily (for 150 mg IDL twice daily) for a 10-day period. No AE or SAE associated with this dosing error was reported.

- Subject [redacted] (IDL + BR): Beginning 07 October 2013, the subject took 3 study drug tables twice daily (for 450 mg IDL twice daily) rather than 1 tablet twice daily (for 150 mg IDL twice daily) for a 9-day period. No AE or SAE associated with this dosing error was reported. Local laboratory samples drawn following this event were within normal parameters.

- Subject [redacted] (IDL + BR): Over the course of 82 days, the subject took 4 more tablets than prescribed: 168 tablets rather than 164 tablets. No AE or SAE associated with this dosing error was reported.

- Subject [redacted] (IDL + BR): On 10 June 2014 the subject was assigned 3 bottles of 100 mg IDL tablets rather than 3 bottles of 150 mg IDL tablets in error. The subject took IDL 100 mg twice daily from 10 June 2014 through 05 August 2014, at which time the error was discovered and the subject was given the correct tablet strength for the remainder of the study. No AE or SAE associated with this dosing error was reported.

- Subject [redacted] (Placebo + BR): Upon reconciliation of study drug, 8 tablets of placebo were noted as missing. The subject may have taken 1 extra tablet each morning for 8 days. No AE or SAE associated with this dosing error was reported. Local laboratory samples drawn following this event were within normal parameters.

- Subject [redacted] (Placebo + BR): From 18 September 2013 through 16 October 2013, the subject took 3 placebo tables twice daily (for a total of 6 tablets daily) rather than 1 placebo tablet twice daily (for a total of 2 tablets daily). The subject reported Grade 3 neutropenia assessed by the investigator as related to study drug and BR, and Grade 3 thrombocytopenia assessed by the investigator as related to bendamustine.

Co-Rapporteur

The missing information has been provided by the MAH and does not raise any concerns with respect to the number of cases and the potential safety issue as for 5 out of 6 cases the dosing errors were not associated with AE or SAE.

Issue resolved

Question 28
The laboratory abnormalities observed in study GS-US-312-0115 related to IDL + BR exposure should be further elucidated with respect to potassium, albumin and phosphate.

Applicant's Response

Further discussion of potassium, albumin, and phosphate laboratory abnormalities is provided below. A summary of the worst postbaseline grades of these abnormalities is provided in Table 20, and a summary of all treatment-emergent serum chemistry abnormalities is provided in the Study GS-US-312-0115 Interim CSR Section 15.1 Table 8.3.2.

Seven subjects (3.4%) in the IDL + BR group had postbaseline increases in potassium (hyperkalemia) of any grade: no subject had a Grade 3 increase and 1 subject (0.5%) had a Grade 4 increase. Eight subjects (3.8%) in the placebo + BR group had postbaseline increases in potassium of any grade: no subject had a Grade 3 increase and 1 subject (0.5%) had a Grade 4 increase.

Fifty-five subjects (26.6%) in the IDL + BR group had postbaseline decreases in potassium (hypokalemia) of any grade: 11 subjects (5.3%) had a Grade 3 decrease and 2 subjects (1.0%) had a Grade 4 decrease. Thirty subjects (14.4%) in the placebo + BR group had postbaseline decreases in potassium of any grade: 7 subjects (3.3%) had a Grade 3 decrease and no subject had a Grade 4 decrease.

Forty-eight subjects (23.2%) in the IDL + BR group had postbaseline hypoalbuminemia of any grade: 3 subjects (1.4%) had a Grade 3 decrease and no subject had a Grade 4 decrease. Thirty subjects (14.4%) in the placebo + BR group had postbaseline hypoalbuminemia of any grade, none of which were Grade 3 or Grade 4.

Forty-seven subjects (22.7%) in the IDL + BR group had postbaseline decreased phosphate (hypophosphatemia) of any grade: 26 subjects (12.6%) had a Grade 3 decrease and no subject had a Grade 4 decrease. Thirty-four subjects (16.3%) in the placebo + BR group had postbaseline decreased phosphate of any grade: 14 subjects (6.7%) had a Grade 3 decrease and no subject had a Grade 4 decrease.

Table 20 GS-US-312-0115: Treatment-Emergent Potassium, Albumin, and Phosphate Laboratory Abnormalities, Worst Grade Post Baseline (Safety Analysis Set)

	IDL + BR (N = 207)	Pl + BR (N = 209)
Worst Grade Abnormality Post Baseline	**n (%)**	**n (%)**
Potassium (Hyperkalemia)		
1	3 (1.4%)	1 (0.5%)
2	3 (1.4%)	6 (2.9%)
3	0	0
4	1 (0.5%)	1 (0.5%)
3 to 4	1 (0.5%)	1 (0.5%)
1 to 4	7 (3.4%)	8 (3.8%)
Potassium (Hypokalemia)		
1	42 (20.3%)	23 (11.0%)
2	0	0
3	11 (5.3%)	7 (3.3%)
4	2 (1.0%)	0
3 to 4	13 (6.3%)	7 (3.3%)
1 to 4	55 (26.6%)	30 (14.4%)
Albumin (Hypoalbuminemia)		
1	26 (12.6%)	9 (4.3%)
2	19 (9.2%)	21 (10.0%)
3	3 (1.4%)	0
4	0	0
3 to4	3 (1.4%)	0
1 to 4	48 (23.2%)	30 (14.4%)
Phosphate (Hypophosphatemia)		
1	0	0
2	21 (10.1%)	20 (9.6%)
3	26 (12.6%)	14 (6.7%)
4	0	0
3 to 4	26 (12.6%)	14 (6.7%)

Worst Grade Abnormality Post Baseline	IDL + BR (N = 207) n (%)	Pl + BR (N = 209) n (%)
1 to 4	47 (22.7%)	34 (16.3%)

Co-Rapporteur
It is noted that in the IDL+BR arm a higher proportion of patients have postbaseline hypokalemia, hypoalbuminemia, hypophosphatemia of which a proportion was grade 3/4. In the case of hypophosphatemia 55% of the gr1-4 events were grade 3 or 4. The MAH does not provide an explanation for the electrolyte disturbances. More information is needed to assess whether hypokalemia, hypoalbuminemia, hypophosphatemia coincided, and on the time to event, time to resolution, and comedication required. Additionally the laboratory abnormalities should be presented in section 4.8. of the SmPC.

Issue not resolved

Question 29

Neutrophil count monitoring is recommended in the SmPC. In the event of severe neutropenia, treatment should be interrupted and may be restarted at a lower dose upon resolution. Noticeable, dose interruption due to neutropenia was only reported in 3.9%, whereas discontinuations or dose reductions were reported < 2% of the cases. As such the applicant is requested to report what measures were taken to address the severe cases of neutropenia (e.g. concomitant medication) and to what extent these cases resolved spontaneously.

Applicant's Response

The guidance provided by the protocol for subjects with Grade 4 neutropenia is to interrupt idelalisib until the neutropenia is Grade 3 or less. The measures taken to address severe cases of neutropenia include use of growth factors as per established clinical guidelines (Study GS-US-312-0115 Protocol Amendment 9, Table 5-6 and Section 5.6.6; {Rizzo 2008, Smith 2006}. Granulocyte Colony-Stimulating Factors (G-CSF) and erythropoietin (filgrastim, PEG-filgrastim, lenograstim) may be administered in response to Grade 4 neutropenia or neutropenic complications. In particular, G-CSF use should be considered if providing hematopoietic support might help to maintain study drug treatment

Grade 4 neutropenia that required IDL interruption occurred in 41 subjects (19.8%) in the IDL + BR group and 19 subjects (9.1%) in the placebo + BR group.

Of the 41 subjects from the IDL + BR group that reported Grade 4 neutropenia, 36 had no change in IDL dose. Six of these 36 subjects with Grade 4 neutropenia also were not treated with concomitant growth factors. The disposition of these subjects follows:

- Subject [redacted], Grade 4 neutropenia started on 03 September 2013 and resolved by 28 October 2013, though this subject had Grade 3 neutropenia on 11 November 2013.
- Subject [redacted], Grade 4 neutropenia started on 11 February 2015 and resolved by 25 March 2015
- Subject [redacted], Grade 4 neutropenia started on 05 May 2014 and resolved by 16 May 2014
- Subject [redacted], Grade 4 neutropenia started on 16 September 2014 and resolved by 30 September 2014.

- Subject [redacted], Grade 4 neutropenia started on 14 April 2014 and resolved to ≤ Grade 3 by 28 April 2014

- Subject [redacted], Grade 4 neutropenia started on 06 November 2014 and resolved to ≤ Grade 3 by 12 November 2014

The other 30 subjects received growth factors as presented in Table 46. In all but two cases, the Grade 4 neutropenia resolved. In those 2 cases, the neutropenia events were ongoing and the subjects ultimately withdrew from study drug. Subject [redacted] was treated with 1 course of filgrastim and 2 courses of pegfilgrastim, and subsequently the patient declined any additional treatment and study drug was not resumed. Subject [redacted] was treated with 6 courses of filgrastim, and was withdrawn from the study by the physician, citing cytopenia and compliance issues (CHMP Listing 4.1).

Table 46 **Study GS-US-312-0115: Subjects with Grade 4 Neutropenia who Received Growth Factors and had No Change in IDL Dose**

Subject	IDL Treatment		Number of Episodes of Neutropenia	Growth Factor Name	Growth Factor Courses Received
	First Exposure	Last Exposure			
[redacted]	12 May 2014	16 Oct 2014	4	filgrastim	5
	02 June 2014	16 Aug 2014	1	filgrastim	4
	09 June 2014	2 May 2016	1	filgrastim	3
	13 Aug 2013	02 May 2016	1	filgrastim	1
	07 Oct 2013	15 Apr 2015	1	pegfilgrastim	1
	06 Aug 2013	28 Sept 2015	2	filgrastim	5
	30 Oct 2013	14 Feb 14	1	filgrastim	1
				pegfilgrastim	2
	18 Nov 13	11 Feb 15	1	pegfilgrastim	1
	2 Jul 13	15 May 14	1	lenograstim	7
	25-Jun-14	2-May-16	1	lenograstim	6
	20 Jan 14	13 Apr 15	1	filgrastim	2
	20 Aug 13	14 Apr 15	4	filgrastim	10
	29 May 14	1 Oct 14	1	filgrastim	6
	01 Jul 14	02 May 16	1	filgrastim	2
	03 Jul 14	28 Nov 14	3	filgrastim	2
				lenograstim	1
				pegfilgrastim	2
	01 Apr 14	02 May 16	1	filgrastim	1
	02 June 14	02 May 16	1	filgrastim	2
	12 Aug 13	05 Jan 16	1	filgrastim	5

Subject	IDL Treatment		Number of Episodes of Neutropenia	Growth Factor Name	Growth Factor Courses Received
	First Exposure	Last Exposure			
[redacted]	05 Mar 14	25 Apr 16	2	filgrastim	1
				lenograstim	4
	29 Aug 13	26 Jan 15	3	pegfilgrastim	5
				filgrastim	1
	20 Feb 14	26 Sept 14	1	filgrastim	3
	24 Mar 14	02 May 16	2	filgrastim	11
	27 Mar 14	27 May 15	3	filgrastim	4
	19 Jun 14	05 Jan 16	1	pegfilgrastim	5
	24 Apr 14	02 May 16	5	filgastim	13
	08 Jul 14	02 May 16	3	filgrastim	1
				pegfilgrastim	3
				lenograstim	1
	22 Jul 14	02 May 16	1	filgrastim	6
	06 Aug 14	16 Nov 15	1	filgrastim	2
	24 Jul 14	10 Nov 15	1	filgrastim	10

Source: Study G8-US-312-0115, Section 16.2.7, Listing 4.1, Listing 4.9.2, Listing 6.11, CHMP Listing 30.3, Listing 30.18

A further 5 subjects in the IDL + BR treatment group had IDL dose interruptions, reductions, or withdrawal due to Grade 4 neutropenia. Two subjects had their IDL dose transiently interrupted due to neutropenia. Subject [redacted] had IDL interrupted from 02 September 2014 to 17 September 2014 due to neutropenia, was not treated with any growth factors, and ultimately had the IDL dose reduced to 100 mg due to an AE of toxic hepatitis. The subject continued the study receiving 100 mg IDL (Study GS-US-312-0115 Interim 1 CSR, Listing 4.9.2). The second subject, [redacted], had a dose interruption due to neutropenia from 28 January 2014 to 04 February 2014, and no treatment with growth factors. After the neutropenia resolved, the dose was increased to 150 mg IDL (Study GS-US-312-0115 Interim 1 CSR, Listing 4.9.2).

Two subjects with Grade 4 neutropenia had their dose reduced to 100 mg. One subject, [redacted] had Grade 4 neutropenia that started at relative Day 601 and ended on Day 608, had the dose of IDL interrupted for 2 days (25 Sept 2015 to 27 Sept 2015) after which the IDL dose was increased to 150 mg of IDL. The IDL dose was subsequently reduced to 100 mg on 27 April 2016 due to neutropenia and remained reduced. Subject [redacted] received 11 courses of filgrastim. Subject [redacted] remained at the 150 mg IDL dose until 18 January 2016, when the dose of IDL was interrupted until 27 April 2016 due to hospitalization with a respiratory infection, and resumed a dose of 100 mg IDL on 27 April 2016. A second subject, [redacted], had Grade 4 neutropenia that started at Day 463 and ended on Day 499, with the dose of IDL reduced to 100 mg on 07 August 2015, due to Grade 4 neutropenia and Grade 2 diarrhea. Subject [redacted] received 1 course of filgrastim (03 August 2015 to 05 August 2015) and the subject continued on the reduced dose of 100 mg IDL (Study GS-US-312-0115 Interim 1 CSR, Listing 1.9.4 and Listing 4.9.2).

Subject [redacted], was given 1 course of pegfilgrastim and 3 courses of filgrastim (last course was completed 06 March 2015), and had IDL withdrawn due to neutropenia on 18 February 2015, and again from 21 February 2015 to 06 March 2015 due to agranulocytosis during hospitalization (Study GS-US-312-0115 Interim 1 CSR, Listing 1.9.4 and Listing 6.1.4). Subject [redacted] discontinued from the study on Day 297 (07 May 2015) due to progressive disease.

Co-Rapporteur

More cases of grade 4 neutropenia occurred in the IDL+BR arm versus the placebo+BR arm. The majority of cases grade 4 neutropenia was managed by the use of growth factors and interruption of idelalisib, although some cases recovered spontaneously. In some cases a subsequent dose reduction was required before resolution of the neutropenia.

The SmPC adequately covers neutropenia in section 4.2., 4.4. and 4.8.

Issue resolved

Question 30
Data cut-off for the interim study report of study GS-US-312-0115 was 02 May 2016, as such a full update of safety from study GS-US-312-0115, including patients in long-term follow-up, is requested.

Applicant's Response

Updated safety results based on a data cutoff date of 31 March 2017 are presented.

A summary of the main results is depicted here. For the full updated safety text please refer to the RSI as provided by the MAH.

Extent of Exposure

Of the 416 subjects randomized in the study, 415 received at least 1 dose of study drug (IDL or placebo) and were evaluable for study drug exposure. The median (Q1, Q3) duration of exposure to IDL in the IDL + BR group was 18.2 (5.8, 30.1) months (range: 0.0 to 54.4 months). The median (Q1, Q3) duration of exposure to placebo in the placebo + BR group was 11.1 (5.8, 16.6) months (range: 0.5 to 28.5 months).

An overall summary of AEs for subjects in the Safety Analysis Set is provided in Table 48. AEs were common in both groups, reported for 207 subjects (100%) in the IDL + BR group and 203 subjects (97.1%) in the placebo + BR group. Serious adverse events (SAEs) were reported for 149 subjects (72.0%) in the IDL + BR group and 94 subjects (45.0%) in the placebo + BR group (Table 48). The subgroup analyses of AEs by gender, age (< 65 years versus ≥ 65 years), and race (white versus nonwhite) were generally consistent with the overall analysis.

Table 21 GS-US-312-0115: Study Drug (Idelalisib/Placebo) Exposure (Safety Analysis Set)

	IDL + BR (N = 207)	Pl + BR (N = 209)	Total (N = 416)
Duration of Exposure to IDL/Placebo (Months)[a]			
N	207	208	415
Mean (StD)	18.4 (13.08)	11.4 (6.47)	14.9 (10.88)
Median	18.2	11.1	13.4
Q1, Q3	5.8, 30.1	5.8, 16.6	5.8, 20.4
Min, Max	0, 54.4	0.5, 28.5	0, 54.4
Cumulative Exposure to IDL/Placebo, n (%)			
≥ 1 Day	207 (100)	208 (99.5)	415 (99.8)
≥ 2 months	186 (89.9)	199 (95.2)	385 (92.5)
≥ 4 months	171 (82.6)	173 (82.8)	344 (82.7)
≥ 6 months	154 (74.4)	154 (73.7)	308 (74.0)
≥ 12 months	127 (61.4)	90 (43.1)	217 (52.2)
≥ 18 months	104 (50.2)	34 (16.3)	138 (33.2)
≥ 24 months	74 (35.7)	8 (3.8)	82 (19.7)
≥ 30 months	52 (25.1)	0	52 (12.5)
≥ 36 months	20 (9.7)	0	20 (4.8)
≥ 42 months	9 (4.3)	0	9 (2.2)
≥ 48 months	1 (0.5)	0	1 (0.2)
Adherence, n (%)[b]			

	IDL + BR (N = 207)	PI + BR (N = 209)	Total (N = 416)
≥ 75%	204 (98.6)	204 (97.6)	408 (98.1)
< 75%	3 (1.4)	4 (1.9)	7 (1.7)

a Duration of exposure (months) = (min [last IDL/Placebo dosing date as captured on study drug completion CRF page, data cutoff date] − first IDL/Placebo dosing date + 1) / 30.4375.
b Adherence (%) = (sum of pills dispensed − sum of pills returned) / (sum over all dosing period of [total daily pills × dosing duration]), taking into account physician-prescribed reductions, escalations, and interruptions.
Source: CHMP Table 30.2.3

Table 48 GS-US-312-0115: Overall Summary of Adverse Events (Safety Analysis Set)

Adverse Event Category	IDL + BR (N = 207) n (%)	PI + BR (N = 209) n (%)
Any AE	207 (100)	203 (97.1)
AE Related to IDL or Placebo	175 (84.5)	125 (59.8)
AE Related to Rituximab	145 (70.0)	145 (69.4)
AE Related to Bendamustine	168 (81.2)	173 (82.8)
Any AE ≥ Grade 3	197 (95.2)	163 (78.0)
AE ≥ Grade 3 Related to IDL or Placebo	145 (70.0)	68 (32.5)
AE ≥ Grade 3 Related to Rituximab	105 (50.7)	83 (39.7)
AE ≥ Grade 3 Related to Bendamustine	148 (71.5)	120 (57.4)
Any SAE	149 (72.0)	94 (45.0)
SAE Related to IDL or Placebo	78 (37.7)	28 (13.4)
SAE Related to Rituximab	48 (23.2)	28 (13.4)
SAE Related to Bendamustine	71 (34.3)	40 (19.1)
AE Leading to IDL/Placebo Dose Reduction	35 (16.9)	13 (6.2)
AE Leading to IDL/Placebo Dose Interruption	126 (60.9)	49 (23.4)
AE Leading to IDL/Placebo Discontinuation	83 (40.1)	31 (14.8)
AE Leading to Death	27 (13.0)	19 (9.1)

SAE = serious adverse event
Relationship to study drug was determined by the investigator; AEs with missing relationships were considered to be related.
Source: CHMP Table 30.3

Most Common Adverse Events

Adverse events reported for ☐ 10% of subjects in either treatment group are summarized by SOC and PT by decreasing frequency in the IDL + BR group in Table 49.

The most commonly reported AEs (reported for ≥ 25% of subjects) by treatment group included the following:

- IDL + BR: neutropenia (132 subjects, 63.8%), diarrhea (90 subjects, 43.5%), pyrexia (90 subjects, 43.5%), nausea (60 subjects, 29.0%), anemia (56 subjects, 27.1%), and cough (52 subjects, 25.1%)

- Placebo + BR: neutropenia (114 subjects, 54.5%), nausea (73 subjects, 34.9%), and pyrexia (63 subjects, 30.1%)

Exposure-Adjusted Incidence Rates of Common Adverse Events

Adverse events reported for ≥ 10% of subjects in either treatment group are summarized by PT and decreasing frequency of the exposure-adjusted incident rate in the IDL + BR group in Table 50.

Adverse events with the highest exposure-adjusted incidence rates (≥ 0.25 events/subject-year) by treatment group included the following:

- IDL + BR: neutropenia (0.99 events/subject-year), pyrexia (0.41 events/subject-year), diarrhea (0.40 events/subject-year), and nausea (0.25 events/subject-year).

- Placebo + BR: neutropenia (0.96 events/subject-year), nausea (0.50 events/subject-year), pyrexia (0.36 events/subject-year), fatigue (0.30 events/subject-year), anemia (0.29 events/subject-year), infusion-related reaction (0.29 events/subject-year), cough (0.27 events/subject-year), diarrhea (0.26 events/subject-year), and thrombocytopenia (0.25 events/subject-year).

Adverse events (any grade) with an exposure-adjusted incidence rate ≥ 0.10 events/subject-year more common in the IDL + BR group included the following: diarrhea, febrile neutropenia, and ALT increased.

Adverse Events of Interest

Tables have been omitted for this section - please refer to Response document of the applicant.

Adverse events of interest for IDL include bowel perforation of any grade, CMV infection of any grade, diarrhea/colitis ≥ Grade 3, febrile neutropenia ≥ Grade 3, infection ≥ Grade 3, PJP of any grade, pneumonitis of any grade, PML of any grade, and rash per Gilead MST ≥ Grade 3.

Bowel Perforation (Any Grade)

Through the data cutoff date for this report (31 March 2017), 1 subject (0.5%) in the IDL + BR group reported an AE of bowel perforation, and no subjects in the placebo + BR group reported AEs of bowel perforation (CHMP Table 30.27).

The exposure-adjusted incidence rate (95% CI) for bowel perforation of any grade was 0.00 events/subject-year (0.00, 0.02) in the IDL + BR group and 0.00 events/subject-year (NEst, 0.02) in the placebo + BR group (Table 53).

The median (Q1, Q3) time to onset of the first event of bowel perforation in the IDL + BR group was 28.3 (28.3, 28.3) weeks (n = 1), and the median (Q1, Q3) time to resolution was 0.1 (0.1, 0.1) weeks (CHMP Table 30.27.7).

No subject in either treatment group had a dose reduction or dose interruption due to bowel perforation. One subject (0.5%) in the IDL + BR group and no subjects in the placebo + BR group discontinued study drug due to bowel perforation (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

No deaths due to bowel perforation were reported in this study (CHMP Table 30.27).

Cytomegalovirus Infection (Any Grade)

The analysis for CMV infection utilized the Medical Dictionary for Regulatory Terms (MedDRA) HLT "cytomegaloviral infections" or the MedDRA PT "cytomegalovirus test positive." Through the data cutoff date for this report (31 March 2017), 14 subjects (6.8%) in the IDL + BR group and 3 subjects (1.4%) in the placebo + BR group reported CMV of any grade (CHMP Table 30.27).

The exposure-adjusted incidence rate (95% CI) for CMV of any grade was 0.04 events/subject-year (0.02, 0.07) in the IDL + BR group and 0.01 events/subject-year (0.00, 0.04) in the placebo + BR group (Table 55).

The median (Q1, Q3) time to onset of the first event of CMV in the IDL + BR group was 18.3 (10.4, 26.4) weeks (n = 14), and the median (Q1, Q3) time to resolution was 3.5 (2.4, 6.0) weeks (n = 12). Among subjects in the placebo + BR group, the median (Q1, Q3) time to onset of the first event of CMV was 7.4 (5.9, 44.0) weeks (n = 3), and the median (Q1, Q3) time to resolution was 14.4 (2.3, 26.4) weeks (n = 2) (CHMP Table 30.27.7).

One subject (0.5%) in the IDL + BR group and no subjects in the placebo + BR had a dose reduction due to CMV. One subject (0.5%) in the IDL + BR group and 1 subject (0.5%) in the placebo + BR group had dose interruptions due to CMV. One subject (0.5%) in the IDL + BR group and 1 subject (0.5%) in the placebo + BR group discontinued study drug due to CMV (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

One death attributed to CMV was reported in the placebo + BR group (CHMP Table 30.27). A narrative for this subject was provided in the Study GS-US-312-0115 Interim 1 CSR Section 15.2.

Diarrhea/Colitis (≥ Grade 3)

The analysis for the AEI of diarrhea/ colitis utilized the MedDRA PTs "diarrhoea" and "colitis." Through the data cutoff date for this report (31 March 2017), 31 subjects (15.0%) in the IDL + BR group and 4 subjects (1.9%) in the placebo + BR group had ≥ Grade 3 diarrhea/colitis (CHMP Table 30.27).

The exposure-adjusted incidence rate (95% CI) for ≥ Grade 3 diarrhea/colitis was 0.10 events/subject-year (0.07, 0.14) in the IDL + BR group and 0.02 events/subject-year (0.01, 0.05) in the placebo + BR group (Table 57).

Data collected through the data cutoff date for this report confirms the late onset of diarrhea/colitis among subjects treated with IDL. The median (Q1, Q3) time to onset of the first ≥ Grade 3 event of diarrhea/colitis in the IDL + BR group based on the data cutoff date for this report was 67.4 (12.6, 109.4) weeks (n = 31) compared with 38.6 (11.1, 79.6) weeks (n = 28) reported in the Interim 1 CSR. The median (Q1, Q3) times to resolution of the highest grade diarrhea/colitis event (≥ Grade 3) were similar: 2.1 (1.0, 5.1) weeks (n = 28) based on the data cutoff date for this report, and 2.0 (0.9, 4.3) weeks (n = 23) reported in the Interim 1 CSR. In the placebo + BR group, the results reported in the Interim 1 CSR were identical to those observed at the data cutoff for this report: the median (Q1, Q3) time to onset of the first ≥ Grade 3 event of diarrhea/colitis was 16.4 (10.4, 29.6) weeks (n = 4), and the median (Q1, Q3) time to resolution of the highest grade diarrhea/colitis event (≥ Grade 3) was 0.9 (0.4, 1.8) weeks (n = 4) (CHMP Table 30.27.7 and Study GS-US-312-0115 Interim 1 CSR Section 11.2.4.2).

In the IDL + BR group, 4 subjects (1.9%) had a dose reduction due to ≥ Grade 3 diarrhea/colitis, 18 subjects (8.7%) had a dose interruption due to ≥ Grade 3 diarrhea/colitis, and 8 subjects (3.9%) discontinued the study drug (IDL) due to ≥ Grade 3 diarrhea/colitis. In the placebo + BR group, no subject had a dose reduction, 2 subjects (1.0%) had a dose interruption due to ≥ Grade 3 diarrhea/colitis, and no subjects discontinued the study drug (placebo) due to ≥ Grade 3 diarrhea/colitis (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

No deaths due to diarrhea/colitis were reported in this study (CHMP Table 30.27).

Febrile Neutropenia (≥ Grade 3)

An imbalance in the incidence of ≥ Grade 3 febrile neutropenia was observed in this study: 50 subjects (24.2%) in the IDL + BR group and 13 subjects (6.2%) in the placebo + BR group (CHMP Table 30.27).

Through the data cutoff date for this report (31 March 2017), the exposure-adjusted incidence rate (95% CI) for ≥ Grade 3 febrile neutropenia was 0.18 events/subject-year (0.13, 0.24) in the IDL + BR group and 0.06 events/subject-year (0.03, 0.11) in the placebo + BR group (Table 59).

The median (Q1, Q3) time to onset of the first event of ≥ Grade 3 febrile neutropenia in the IDL + BR group was 10.0 (3.0, 22.0) weeks (n = 50), and the median (Q1, Q3) time to resolution was 1.1 (0.7, 1.3) weeks (n = 49). Among subjects in the placebo + BR group, the median (Q1, Q3) time to onset of the first event of ≥ Grade 3 febrile neutropenia was 4.1 (2.1, 18.6) weeks (n = 13), and the median (Q1, Q3) time to resolution was 1.1 (0.9, 1.6) weeks (n = 12) (CHMP Table 30.27.7).

In the IDL + BR group, 2 subjects (1.0%) had a dose reduction, 15 subjects (7.2%) had a dose interruption, and 5 subjects (2.4%) discontinued the study drug (IDL) due to ≥ Grade 3 febrile neutropenia. In the placebo + BR group, no subject had a dose reduction, 3 subjects (1.4%) had a dose interruption, and 2 subjects (1.0%) discontinued the study drug (placebo) due to ≥ Grade 3 febrile neutropenia (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

No deaths among subjects in the IDL + BR group due to ≥ Grade 3 febrile neutropenia were reported in this study. One death (0.5%) among subjects in the placebo + BR group due to ≥ Grade 3 febrile neutropenia was reported (CHMP Table 30.27). A narrative for this subject was provided in the Study GS-US-312-01115 Interim 1 CSR Section 15.2.

Infection (≥ Grade 3)

For the AEI of ≥ Grade 3 infection, the analysis utilized the MedDRA SOC "Infections and Infestations" and the MedDRA PT "febrile neutropenia." Through the data cutoff date for this report (31 March 2017), 112 subjects (54.1%) in the IDL + BR group and 60 subjects (28.7%) in the placebo + BR group reported ≥ Grade 3 infection (CHMP Table 30.27).

The exposure adjusted incidence rate (95% CI) for ≥ Grade 3 infection was 0.50 events/subject year (0.41, 0.60) in the IDL + BR group and 0.32 events/subject year (0.24, 0.41) in the placebo + BR group (Table 62).

The median (Q1, Q3) time to onset of the first event of ≥ Grade 3 infection in the IDL + BR group was 14.2 (5.3, 29.0) weeks (n = 112), and the median (Q1, Q3) time to resolution was 1.3 (0.9, 2.6) weeks (n = 104). Among subjects in the placebo + BR group, the median (Q1, Q3) time to onset of the first event of ≥ Grade 3 infection was 13.1 (4.1, 26.6) weeks (n = 60), and the median (Q1, Q3) time to resolution was 1.4 (1.0, 3.6) weeks (n = 50) (CHMP Table 30.27.7).

In the IDL + BR group, 5 subjects (2.4%) had a dose reduction due to ≥ Grade 3 infection, 38 subjects (18.4%) had a dose interruption due to ≥ Grade 3 infection, and 20 subjects (9.7%) discontinued the study drug (IDL) due to ≥ Grade 3 infection. In the placebo + BR group, 1 subject (0.5%) had a dose reduction due to ≥ Grade 3 infection, 12 subjects (5.7%) had a dose interruption due to ≥ Grade 3 infection, and 12 subjects (5.7%) discontinued the study drug (placebo) due to ≥ Grade 3 infection (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

Fourteen subjects (6.8%) in the IDL + BR group and 10 subjects (4.8%) in the placebo + BR group died due to ≥ Grade 3 infections (CHMP Table 30.27). Narratives for these subjects were provided in the Study GS US 312 0115 Interim 1 CSR Section 15.2.

Pneumocystis jirovecii Pneumonia (Any Grade)

For the AEI of PJP, the analysis utilized the MedDRA HLT "Pneumocystis Infections." Through the data cutoff date for this report (31 March 2017), 4 subjects (1.9%) in the IDL + BR group and no subjects in

the placebo + BR group reported PJP of any grade (CHMP Table 30.27). Narratives for subjects with PJP events of any grade were provided in the Study GS US 312 0115 Interim 1 CSR Section 15.2.

The exposure adjusted incidence rate (95% CI) for PJP of any grade was 0.01 events/subject year (0.00, 0.03) in the IDL + BR group and 0.00 events/subject year (NEst, 0.02) in the placebo + BR group (Table 64).

The median (Q1, Q3) time to onset of the first event of PJP of any grade in the IDL + BR group was 31.0 (21.6, 48.7) weeks (n = 4), and the median (Q1, Q3) time to resolution was 3.1 (2.6, 3.9) weeks (n = 4). No subjects in the placebo + BR group reported PJP of any grade (CHMP Table 30.27.7).

No subject in either treatment group had a dose reduction or study drug discontinuation due to PJP. Two subjects (1.0%) in the IDL + BR and no subjects in the placebo + BR group had a dose interruption due to PJP (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

Pneumonitis (Any Grade)

Through the data cutoff date for this report (31 March 2017), 8 subjects (3.9%) in the IDL + BR group and 2 subjects (1.0%) in the placebo + BR group reported pneumonitis of any grade (CHMP Table 30.27).

The exposure adjusted incidence rate (95% CI) for pneumonitis of any grade was 0.02 events/subject year (0.01, 0.05) in the IDL + BR group and 0.01 events/subject year (0.00, 0.03) in the placebo + BR group (Table 66).

The median (Q1, Q3) time to onset of the first event of pneumonitis of any grade in the IDL + BR group was 48.4 (23.1, 64.1) weeks (n = 8), and the median (Q1, Q3) time to resolution was 2.2 (1.1, 7.6) weeks (n = 4). In the placebo + BR group, the median (Q1, Q3) time to onset of the first event of pneumonitis of any grade was 31.9 (24.6, 39.1) weeks (n = 2), and the time to resolution was 9.1 weeks (n = 1) (CHMP Table 30.27.7).

One subject (0.5%) in the IDL + BR group and no subjects in the placebo + BR group had a dose reduction due to pneumonitis. One subject (0.5%) in the IDL + BR and 1 subject (0.5%) in the placebo + BR group had a dose interruption due to pneumonitis. Three subjects (1.4%) in the IDL + BR group and no subjects in the placebo + BR group discontinued the study drug due to pneumonitis (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

One subject (0.5%) in the IDL + BR group and no subjects in the placebo + BR group died due to pneumonitis (CHMP Table 30.27). A narrative for this subject was provided in the Study GS US 312 0115 Interim 1 CSR Section 15.2.

Progressive Multifocal Leukoencephalopathy

No subject reported PML during this study.

Rash per Gilead MST (≥ Grade 3)

Rash was defined per Gilead MST and included the following terms: dermatitis exfoliative, drug eruption, drug reaction with eosinophilia and systemic symptoms, eosinophilic pustular folliculitis, erythema nodosum, erythema multiforme, neurodermatitis, prurigo, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbiliform, rash papular, rash pruritic, rash pustular, rash vesicular, skin disorder, Stevens Johnson syndrome (SJS), and toxic skin eruption.

Through the data cutoff date for this report (31 March 2017), 14 subjects (6.8%) in the IDL + BR group and no subjects in the placebo + BR group had ≥ Grade 3 rash per MST (CHMP Table 30.27).

The exposure adjusted incidence rate (95% CI) for ≥ Grade 3 rash per MST was 0.04 events/subject year (0.02, 0.07) in the IDL + BR group and 0.00 events/subject year (NEst, 0.02) in the placebo + BR group (Table 68).

The median (Q1, Q3) time to onset of the first ≥ Grade 3 event of rash per MST in the IDL + BR group was 8.5 (3.4, 11.6) weeks (n = 14), and the median (Q1, Q3) time to resolution was 8.0 (2.1, 10.1) weeks (n = 11). No ≥ Grade 3 rash per MST AEs were reported in the placebo + BR group (CHMP Table 30.27.7).

Two subjects (1.0%) in the IDL + BR group and no subjects in the placebo + BR group had a dose reduction due to ≥ Grade 3 rash per MST. Five subjects (2.4%) in the IDL + BR group and no subjects in the placebo + BR group had a dose interruption due to ≥ Grade 3 rash per MST. Three subjects (1.4%) in the IDL + BR group and no subjects in the placebo + BR group discontinued study drug due to ≥ Grade 3 rash per MST (CHMP Tables 30.27.3, 30.27.4, and 30.27.5).

One subject (0.5%) in the IDL + BR group and no subjects in the placebo + BR group died due to rash per MST (CHMP Table 30.27). A narrative for this event of SJS was provided in the Study GS US 312 0115 Interim 1 CSR Section 15.2.

Cases of SJS and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported when IDL was administered concomitantly with other medications associated with these syndromes. In addition to the event of Grade 5 SJS, one additional subject in the IDL + BR group reported Grade 3 SJS (CHMP Table 30.7); concomitant medications included azithromycin followed by levofloxacin, acyclovir, furosemide, and omeprazole. No case of TEN was reported in this study.

Serious Adverse Events

Serious adverse events that were reported for ≥ 2% of subjects in either treatment group are summarized in Table 70.

Serious adverse events were common in both treatment groups, reported for 149 subjects (72.0%) in the IDL + BR group and 94 subjects (45.0%) in the placebo + BR group. SAEs were typical of the population. The most frequently reported SAEs included the following:

- IDL + BR group: febrile neutropenia (44 subjects, 21.3%), pneumonia (36 subjects, 17.4%), and pyrexia (25 subjects, 12.1%)

- Placebo + BR group: pneumonia (16 subjects, 7.7%), pyrexia (11 subjects, 5.3%), and febrile neutropenia (10 subjects, 4.8%)

Study drug-related SAEs were reported for 78 subjects (37.7%) in the IDL + BR group and 28 subjects (13.4%) in the placebo + BR group. SAEs assessed by the investigator as related to study drug (IDL/placebo) that occurred in ≥ 2% of subjects are summarized in Table 71.

The most frequently reported study drug-related SAEs included the following:

- IDL + BR group: febrile neutropenia (21 subjects, 10.1%), pneumonia (12 subjects, 5.8%), and diarrhea (10 subjects, 4.8%)

- Placebo + BR group: pyrexia (5 subjects, 2.4%), pneumonia (4 subjects, 1.9%), and febrile neutropenia (3 subjects, 1.4%)

Serious adverse events assessed by the investigator as related to rituximab were reported for 48 subjects (23.2%) in the IDL + BR group and 28 subjects (13.4%) in the placebo + BR group (CHMP Table 30.25). The most frequently reported rituximab-related SAEs (reported for ≥ 2% of subjects) included the following:

- IDL + BR group: febrile neutropenia (11 subjects, 5.3%) and pneumonia (7 subjects, 3.4%)

- Placebo + BR group: no rituximab-related SAEs were reported for ≥ 2% of subjects

Serious adverse events assessed by the investigator as related to bendamustine were reported for 71 subjects (34.3%) in the IDL + BR group and 40 subjects (19.1%) in the placebo + BR group (CHMP Table 30.26). The most frequently reported bendamustine-related SAEs (reported for ≥ 2% of subjects) included the following:

- IDL + BR group: febrile neutropenia (28 subjects, 13.5%), pneumonia (9 subjects, 4.3%), neutropenia (7 subjects, 3.4%), and pyrexia (6 subjects, 2.9%)

- Placebo + BR group: febrile neutropenia (6 subjects, 2.9%), pyrexia (6 subjects, 2.9%), and pneumonia (5 subjects, 2.4%)

Table 70 GS-US-312-0115: Serious Adverse Events Reported for ≥ 2% of Subjects in Either Treatment Group (Safety Analysis Set)

Preferred Term, n (%)	IDL + BR (N = 207)	PI + BR (N = 209)
Number of Subjects (%) with any SAE	149 (72.0)	94 (45.0)
Febrile Neutropenia	44 (21.3)	10 (4.8)
Pneumonia	36 (17.4)	16 (7.7)
Pyrexia	25 (12.1)	11 (5.3)
Sepsis	11 (5.3)	4 (1.9)
Diarrhoea	13 (6.3)	1 (0.5)
Anaemia	8 (3.9)	5 (2.4)
Lower Respiratory Tract Infection	7 (3.4)	5 (2.4)
Neutropenia	9 (4.3)	3 (1.4)
Neutropenic Sepsis	3 (1.4)	6 (2.9)
Respiratory Tract Infection	4 (1.9)	5 (2.4)
Urinary Tract Infection	6 (2.9)	3 (1.4)
Pulmonary Embolism	2 (1.0)	5 (2.4)
Bronchitis	1 (0.5)	5 (2.4)
Colitis	5 (2.4)	1 (0.5)
Septic Shock	5 (2.4)	1 (0.5)
Squamous Cell Carcinoma	1 (0.5)	5 (2.4)

AEs were classified according to MedDRA, Version 20.0.
Subjects who experienced multiple events within the same PT were counted once per PT.
PTs are presented by descending order of total frequencies.
Source: CHMP Table 30.23

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Table 71 GS-US-312-0115: Serious Adverse Events Reported for ≥ 2% of Subjects in Either Treatment Group Considered Related to Study Drug (Safety Analysis Set)

Preferred Term, n (%)	IDL + BR (N = 207)	PI + BR (N = 209)
Number of Subjects (%) with SAEs Related to IDL/PI	78 (37.7)	28 (13.4)
Febrile Neutropenia	21 (10.1)	3 (1.4)
Pneumonia	12 (5.8)	4 (1.9)
Diarrhoea	10 (4.8)	1 (0.5)
Colitis	5 (2.4)	1 (0.5)
Pyrexia	4 (1.9)	5 (2.4)

AEs were classified according to MedDRA, Version 20.0.
Subjects who experienced multiple events within the same PT were counted once per PT.
Relationship to study drug was determined by investigator; AEs with missing relationships were considered to be related.
Source: CHMP Table 30.24

Deaths

Through the data cutoff date for this report, 161 subject deaths were reported, 70 during the study (deaths between randomization and within 30 days following end of study) and 91 during LTFU (CHMP Table 30.46). In the IDL + BR group, 75 subjects (36.2%) died: 38 subjects (18.4%) who died during the study and 37 subjects (17.9%) who died during LTFU. In the placebo + BR group, 86 subjects (41.1%) died: 32 subjects (15.3%) who died during the study and 54 subjects (25.8%) who died during LTFU.

Adverse events leading to death were consistent with a population having advanced CLL. AEs leading to death reported for ≥ 2 subjects in either treatment group included the following:

- IDL + BR group: pneumonia (5 subjects, 2.4%), sepsis (3 subjects, 1.4%), and septic shock (2 subjects, 1.0%) (CHMP Table 30.21)
- Placebo + BR group: pneumonia (5 subjects, 2.4%), sepsis (2 subjects, 1.0%), and acute myocardial infarction (2 subjects, 1.0%) (CHMP Table 30.21)

Discontinuations Due To Adverse Events

AEs Leading to Discontinuation and Interruption of Study Drug (IDL/placebo)

A summary of AEs that led to discontinuation of study drug (IDL/placebo) in ≥ 2 subjects in either treatment group is summarized in Table 71. Overall, 83 subjects (40.1%) in the IDL + BR group and 31 subjects (14.8%) in the placebo + BR group discontinued study drug due to an AE. Overall, 126 subjects (60.9%) in the IDL + BR group and 49 subjects (23.4%) in the placebo + BR group had AEs leading to dose interruption of study drug (IDL/placebo). AEs leading to interruption of study drug for ≥ 5% of subjects in the IDL + BR group included the following: diarrhea (32 subjects, 15.5%), ALT increased (19 subjects, 9.2%), febrile neutropenia (15 subjects, 7.2%), and pneumonia (12 subjects, 5.8%). No AE led to interruption of study drug in the placebo + BR group for ≥ 5% of subjects (CHMP Table 30.13).

Overall, 35 subjects (16.9%) in the IDL + BR group and 13 subjects (6.2%) in the placebo + BR group had AEs leading to dose reduction of study drug (IDL/placebo). AEs leading to dose reduction for ≥ 2% of subjects in the IDL + BR group included the following: diarrhea (9 subjects, 4.3%) and ALT increased (6 subjects, 2.9%). No AE led to dose reduction in the placebo + BR group for ≥ 2% of subjects (CHMP Table 30.12).

AEs Leading to Discontinuation and Interruption of Rituximab

Adverse events leading to rituximab discontinuation are summarized in CHMP Table 30.17, and AEs leading to interruption of rituximab dosing are summarized in CHMP Table 30.16.

AEs Leading to Discontinuation and Interruption of Bendamustine

Adverse events leading to bendamustine discontinuation are summarized in CHMP Table 30.19, and AEs leading to interruption of bendamustine dosing are summarized in CHMP Table 30.18.

Table 72 **GS-US-312-0115: Adverse Events Leading to Study Drug Discontinuation for ≥ 2 Subjects (Safety Analysis Set)**

Preferred Term, n (%)	IDL + BR (N = 207)	PI + BR (N = 209)
No. Subjects (%) with AEs Leading to IDL/PI Discontinuation	83 (40.1)	31 (14.8)
Pneumonia	11 (5.3)	4 (1.9)
Diarrhoea	13 (6.3)	0
Febrile Neutropenia	5 (2.4)	2 (1.0)
Pyrexia	4 (1.9)	2 (1.0)
Sepsis	3 (1.4)	2 (1.0)
Anaemia	3 (1.4)	1 (0.5)
Colitis	3 (1.4)	0
Hepatocellular Injury	3 (1.4)	0
Neutropenia	3 (1.4)	0
Pneumonitis	3 (1.4)	0
Thrombocytopenia	3 (1.4)	0
Abdominal Pain	2 (1.0)	0
Acute Myocardial Infarction	0	2 (1.0)
Asthenia	0	2 (1.0)
Autoimmune haemolytic anaemia	0	2 (1.0)
Cough	2 (1.0)	0
Myelodysplastic syndrome	2 (1.0)	0
Nausea	2 (1.0)	0
Pancreatitis	2 (1.0)	0
Pancytopenia	2 (1.0)	0
Vomiting	2 (1.0)	0

AEs were classified according to MedDRA, Version 20.0.
Subjects who experienced multiple events within the same PT were counted once per PT.
Source: CHMP Table 30.15

Clinical Laboratory Evaluations

Not presented in this report, please refer to Response document

Co-Rapporteur

An update of approximately 11 months (previous data-cut: 2 May 2016, current DBL: 31 March 2017) was submitted. This data showed an increased number of subjects with an IDL+BR exposure of >24 months from 51 to 74 subjects (35.7%), while the exposure of the control arm was not increased. In general, the updated safety information is consistent with the known safety profile of idelalisib.

The increased exposure leads to more AEs leading to IDL dose interruption (122 previous DBL to 126 current DLB) and IDL discontinuation (68 previous DBL towards 83 current DBL). The AE leading to IDL discontinuation that showed the highest increase in number (≥2) was diarrhoea (increase from 5 towards 12 subjects) and 2 additional cases of febrile neutropenia compared to the previous data-cut.

Among subjects in the IDL + BR group, 126 of 207 subjects (60.9%) had an AE that led to IDL dose interruption, an increase of 4 subjects since previous DBL. Adverse events leading to IDL dose interruption reported for ≥ 5% of subjects included diarrhoea (32 subjects, 15.5%), ALT increased (19 subjects, 9.2%), febrile neutropenia (15 subjects, 7.2%), and pneumonia (11 subjects, 5.3%). The 4 additional cases all had a dose interruption due to AE diarrhoea.

Assessment of the update on the number of death on study and in long-term follow up might be hampered by the number of patients that discontinued either on study or during long term follow up. This is discussed in more detail in efficacy Q2(above). The AEs leading to death show similar results as during the previous round.

In conclusion, it is noticeable that the safety update with an additional 11 months of exposure to IDL shows an higher than expected increase in number of subjects with a dose interruption of dose discontinuation due to diarrhoea. The applicant is requested to discuss this finding taking in to account the time to discontinuation or dose interruption due to diarrhoea and the duration of the AE of diarrhoea should be reported.

Issue not resolved.

Question 31
Is there a relationship between degree of neutropenia and onset of pneumonia, colitis and pyrexia?

Applicant's Response

The grade of neutropenia within 7 days prior to the onset of pneumonia, diarrhea/colitis, or pyrexia is shown in Table 78. No apparent relationship between degree of neutropenia and onset of diarrhea/colitis or pyrexia was observed.

Table 78 **GS-US-312-0115: Relationship between Neutropenia Severity Grade and Onset of Pneumonia, Diarrhea/Colitis, and Pyrexia (Safety Analysis Set)**

	IDL + BR (N = 207)	Placebo + BR (N = 209)
ANC Grade 0, n (%)		
Any Grade Pneumonia	12/50 (24.0)	8/27 (29.6)
Any Grade Diarrhea/Colitis	24/86 (27.9)	13/49 (26.5)
Any Grade Pyrexia	25/90 (27.8)	13/63 (20.6)
ANC Grade 1, n (%)		
Any Grade Pneumonia	1/50 (2.0)	2/27 (7.4)
Any Grade Diarrhea/Colitis	6/86 (7.0)	5/49 (10.2)
Any Grade Pyrexia	6/90 (6.7)	11/63 (17.5)
ANC Grade 2, n (%)		
Any Grade Pneumonia	1/50 (2.0)	3/27 (11.1)
Any Grade Diarrhea/Colitis	6/86 (7.0)	4/49 (8.2)
Any Grade Pyrexia	10/90 (11.1)	9/63 (14.3)
ANC Grade 3, n (%)		
Any Grade Pneumonia	3/50 (6.0)	1/27 (3.7)
Any Grade Diarrhea/Colitis	4/86 (4.7)	2/49 (4.1)
Any Grade Pyrexia	6/90 (6.7)	3/63 (4.8)
ANC Grade 4, n (%)		
Any Grade Pneumonia	6/50 (12.0)	1/27 (3.7)
Any Grade Diarrhea/Colitis	3/86 (3.5)	2/49 (4.1)
Any Grade Pyrexia	4/90 (4.4)	3/63 (4.8)

ANC = absolute neutrophil count
Numerator is the number of subjects with ANC Grade X (X = 0 to 4), within 7 days prior to AE onset.
Denominator is the number of subjects with specific AEs.
Source: CHMP Table 31

Co-Rapporteur
Issue solved.

5. RMP

32. Please revise the safety concerns:

For important identified risks; rash and SJS may be replaced with "Severe toxic skin reactions, including SJS and TEN" and replace transaminase elevations with "severe transaminase elevations", similarly neutropenia with "severe neutropenia".

MAH's Response

Three important identified risks have been revised in the EU-RMP. "Rash" and "SJS/TEN" were merged and replaced with "severe toxic skin reactions, including SJS and TEN," "transaminase elevation" was amended to "hepatotoxicity including transaminase elevation and hepatocellular injury," and "neutropenia" was amended to "severe neutropenia." Consistent with the request of the Pharmacovigilance Risk Assessment Committee (PRAC) during assessment of PSUR/PBRER #5 (reporting period 23 July 2016 to 22 January 2017), the important identified risk of "transaminase elevation" has been amended to "hepatotoxicity including transaminase elevation and hepatocellular injury".

Rapporteur

Resolved

Annex 2: 2nd Request for Supplementary Information

Clinical efficacy aspects

Major objection

A favourable effect on PFS is not accepted as the main outcome measure in support of the proposed indication. Maintenance therapy vs. placebo was part of the experimental regimen and progression on therapy has a different meaning to progression on placebo, i.e. results are biased in favour of the experimental arm. Therefore a favourable treatment effect beyond PFS1 is needed.

In addition and of major importance, the toxicity of idelalisib add-on mandates reliable and stable OS data for a proper benefit/risk assessment.

PFS2 data as reported appear non-reliable due to the very high event rates in terms of deaths (81% vs. 64%). Furthermore next-line therapy is reported as unknown in 30 to 40% of patients (vs. yes or no).

- Time to first and time to second next-line therapy should be reported based on the most recent study update. In the time to next-line analyses, deaths and missingness/lost to follow-up/unknown should be detailed.

OS: At event rates of 36 and 41% and a change in the OS HR from 0.67 (95% CI 0.47; 0.96) in the prior OS analyses to 0.8 (95% CI 0.59; 1.09) in the OS analysis of March 2017, data appear unstable and are moving in a non-favourable direction. Thus OS data are not considered reasonably mature and stable.

Based on the May 2016 cut-off it was found that 30 patients out of 84 individuals (36%) eligible for long-term follow up (LTFU) declined participation or left LTFU in the idelalisib arm and similarly 24/116 (21 %) in the control group. This constitutes a major concern as regards reliability of OS data.

- LFTU data should be updated using the March 2017 (or later) cut-off.
- The impact of informative censoring on OS is requested to be investigated by additional analyses, not only the possible informative censoring within 26 (IDL+BR) vs 19 (placebo + BR) patients that did not enter the long term follow-up, but also for the 4 (IDL+BR) vs 6 (placebo+BR) subjects, that discontinued during the long-term follow-up (see also RSI#3). Preferably, this would include a "worst case" scenario in which the events excluded due to informative censoring are imputed as "death".

Efficacy

1. To further clarify the shift in HR as observed for the OS analysis (02MAY2016 analysis versus 31MAR2017 analysis). The applicant is requested to investigate the following:

   a) Whether the shift in point estimates of the HR from 0.67 to 0.8 could be caused by the 37-43 months period in which only 10-15% of patients are at risk.

   b) As noted in the response to RSI#14, Gilead stopped the study early due to efficacy and treatment assignments were unblinded study-wide on 16 November 2015. The Applicant is asked to report whether patients in the placebo arm crossed over to the experimental arm and if so, to discuss its impact.

2. The applicant is asked to present the type of subsequent therapies. In order to improve interpretation of time to next subsequent treatment data, a sensitivity analysis for informative censoring should be performed, as reasons for censoring are not provided (72% in the IDL=BR arm versus 56.9%in the placebo + BR arm).

3. Please submit survival data (including medians) by predefined subgroups based on the latest survival cut-off.

Safety

4. In light of the increased numbers of patients with hypokalemia, hypoalbuminemia, and hypophosphatemia in the IDL+BR arm, more information is needed to assess whether these specific electrolyte disturbances coincided, the time to event, time to resolution, and comedication required. Additionally, the laboratory abnormalities need to be presented in section 4.8. of the SmPC.

5. The safety update of study GS-US-0312-0115 with an additional 11 months of exposure to IDL shows a higher than expected increase in number of subjects with a dose interruption or dose discontinuation due to diarrhoea. The applicant is requested to discuss.

6. Please report in tables and per induction phase and per maintenance phase, ADR as reported in table 2 of section 4.8 of the SPC, deaths, SAE and grade ≥3 or more AEs and discontinuations due to AEs.

Assessment of the responses to the 2nd Request for Supplementary Information

In response to the second list of outstanding issues, the MAH decided to withdraw the application for the extension of indication for Zydelig (idelalisib) in combination with bendamustine and rituximab for the treatment of adult patients with relapsed chronic lymphocytic leukemia (CLL).

The withdrawal is based on the CHMP consideration that, whilst the study met the primary endpoint for progression-free survival and demonstrated a clinically meaningful benefit in overall survival, longer term data are required to allow the committee to conclude on a positive benefit-risk evaluation.

Annex 3: Product Information annotated with (Co)Rapporteur(s) comments

This Annex could also be circulated as a separate document.