21 July 2016
EMA/CHMP/657576/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zydelig

International non-proprietary name: idelalisib

Procedure No. EMEA/H/C/003843/II/0011

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukemia
CSR	clinical study report
CYP3A	cytochrome P450 3A
DOR	duration of response
eCLcr	estimated creatinine clearance
EU	European Union
HR	hazard ratio
Id	idelalisib (Zydelig®)
idelalisib	Zydelig®
IGHV	immunoglobulin heavy chain variable region
iNHL	indolent non-Hodgkin lymphoma
IRC	independent review committee
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
KPS	Karnofsky Performance Status
LD	Longest diameter
LNR	lymph node response
LPD	longest perpendicular diameter
LVD	longest vertical dimension
m	Module
MedDRA	Medical Dictionary for Regulatory Activities
MST	Gilead Medical Search Term
N or n	number of subjects in a population (N) or subset (n)

NR	not reached
O	ofatumumab
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic(s)
Pl	placebo
PP	per protocol
PT	preferred term
Q1	first quartile
Q3	third quartile
R	rituximab
SAE	serious adverse event
SAP	statistical analysis plan
SPD	sum of the products of the perpendicular diameters of measured lymph nodes
SOC	system organ class
ULN	upper limit of normal
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd submitted to the European Medicines Agency on 26 June 2015 an application for a variation.

The following variation was requested:

Variation requested		**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

Extension of Indication for Zydelig to include the combination of idelalisib with ofatumumab; 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 for United Kingdom and Ireland in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision 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 applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Kristina Dunder CHMP Co-Rapporteur: N/A
PRAC Rapporteur: Rafe Suvarna

Timetable	Actual dates
Submission date	26 June 2015
Start of procedure	25 July 2015
CHMP Rapporteur's preliminary assessment report circulated on	21 September 2015
PRAC Rapporteur's preliminary assessment report circulated on	21 September 2015
PRAC RMP advice and assessment overview adopted by PRAC	8 October 2015
CHMP Rapporteur's updated assessment report circulated on	15 October 2015
Request for supplementary information and extension of timetable adopted by the CHMP on	22 October 2015
MAH's responses submitted to the CHMP on	17 November 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	23 November 2015
PRAC RMP advice and assessment overview adopted by PRAC	3 December 2015
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	7 December 2015
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	14 December 2015
The CHMP adopted a report on similarity of Zydelig with Imbruvica, Gazyvaro and Arzerra (Appendix 1) on	17 December 2015
Second request for supplementary information and extension of timetable adopted by the CHMP on	17 December 2015
MAH's responses submitted to the CHMP on	26 January 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	2 February 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	10 February 2016
PRAC RMP advice and assessment overview adopted by PRAC	11 February 2016
CHMP opinion:	25 February 2016
CHMP revised opinion*	21 July 2016

* opinion revised to take into account the outcome of EMEA/H/A-20/1439/C/003843/0023

2. Scientific discussion

2.1. Introduction

Zydelig (idelalisib) is a small molecule inhibitor of the catalytic subunit p110δ isoform of phosphatidylinositol 3-kinase (PI3K) that targets a key pathway implicated in the pathobiology of chronic lymphocytic leukemia (CLL). Zydelig was approved by the European Commission on 18 September 2014 as monotherapy and in combination with rituximab. Rituximab is a chimeric anti-CD20 monoclonal antibody which binds primarily the large extracellular loop of CD20. It is from the

same class of type I anti-CD20 antibodies as ofatumumab, a human monoclonal antibody (IgG1) that binds to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule. Thus, while both rituximab and ofatumumab bind to CD20, they recognise and bind to different epitopes on the CD20 molecule. The binding of rituximab and ofatumumab is thought to induce cell death of CD20 positive cells, primarily through complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC), and less by apoptosis. Type I and type II anti-CD20 have different molecular properties and are thought to act through different mechanisms of action. While Type I anti-CD20 antibodies, which include rituximab, ofatumumab, ublituxumab, ocaratuzumab are insoluble in lipid rafts, and binding to ligand mainly leads to clustering and efficient complement -dependent cell death (CDC) and ADCC (antibody-dependent cell-mediated cytotoxicity), Type II anti-CD20 antibodies, such as tositumomab and obinutuzumab, are found in detergent soluble fractions and are thought to act by recruiting effector FcR expressing cells which will then mediate ADCC and phagocytosis.

The combination of idelalisib with rituximab was shown to be superior to rituximab alone for PFS and OS in frail patients with advanced CLL. Subjects with cytogenetic factors associated with poor prognosis, including 17p deletion and/or TP53 mutation, also had significant improvement in PFS and OS. Hence, the combination of idelalisib + ofatumumab, another anti-CD20 antibody, was investigated in study GS-US-312-0119, a Phase 3, multicenter, randomized, open-label, parallel-group evaluating the efficacy and safety of patients treated with idelalisib + ofatumumab compared to ofatumumab treatment in previously treated CLL patients.

Zydelig was approved in the EU for the following indications:

- Zydelig is indicated in combination with rituximab for the treatment of adult patients with CLL:
    - who have received at least 1 prior therapy, or
    - as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy.
- Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to 2 prior lines of treatment.

The MAH applied for the following indication:

- Zydelig is indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with CLL:
    - who have received at least 1 prior therapy, or
    - as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Ecotoxicity / environmental risk assessment

An ERA was not submitted in the context of this variation. The applicant justified the lack of an ERA as the proposed indication is for a new combination within the currently approved CLL patient population. Therefore, it is not anticipated that there would be a significant increase in the extent of use and thus, unlikely to lead to an increase in environmental exposure.

2.2.2. Discussion on non-clinical aspects

The CHMP considers that the lack of non-clinical studies in the submission is acceptable as non-clinical data for ofatumumab has been characterised since it has been previously approved for a CLL indication. In addition, the patient population is a subset of CLL patients as the one already indicated with rituximab+ idelalisib. There were no changes made to section 5.3 of the SmPC.

2.2.3. Conclusion on the non-clinical aspects

The justification for not submitting an ERA in this application is acceptable as the data suggest that there will be no significant increase in environmental exposure to idelalisib as the target population in the indication is the same as previously. Hence, idelalisib is not expected to pose an increased risk to the environment. The lack of non-clinical studies is considered justified.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Description of Study
Efficacy and Safety	
GS-US-312-0119	Phase 3, randomized, controlled study evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL
GS-US-312-0116	Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with rituximab for previously treated CLL
GS-US-312-0117	Phase 3, double-blind extension study evaluating the efficacy and safety of 2 different dose levels of single-agent idelalisib for previously treated CLL; a companion study to Study GS-US-312-0116
Safety	
101-02	Phase 1 sequential dose-escalation study to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of idelalisib in subjects with selected, relapsed or refractory hematologic malignancies
101-07	Phase 1 study of idelalisib with chemotherapeutic agents, immunomodulatory agents, and ant-CD20 monoclonal antibodies in subjects with relapsed or refractory indolent B-cell non-Hodgkin lymphoma, mantle cell lymphoma, or CLL
101-08	Phase 2 single-arm study of idelalisib alone (Cohort 2) and with rituximab (Cohort 1) in elderly subjects with previously untreated CLL or SLL
101-99	Phase 1/2 extension study of idelalisib in subjects with hematologic malignancies from Studies 101-08, 101-07, and 101-02

CLL = chronic lymphocytic leukemia; CSR = clinical study report

2.3.2. Pharmacokinetics

As the idelalisib PK profile has been well characterized in Phase 1 studies, limited plasma sampling was performed in study GS-US-312-0119.

Table 1: Idelalisib plasma concentrations following idelalisib 150 mg twice daily in combination therapy with ofatumumab for previously treated CLL subjects – Study GS-US-312-0119

	Sampling Time					
	Week 3		Week 12		Week 24	
Analyte	predose	1.5 hours postdose	predose	1.5 hours postdose	predose	1.5 hours postdose
Idelalisib (ng/mL)						
N	153	149	126	128	112	114
Median (Q1, Q3)	420 (239, 669)	2240 (1760, 2950)	302.5 (186, 502)	2070 (1585, 2795)	372.5 (204, 724)	2070 (1410, 2730)
GS-563117 (ng/mL)						
N	156	150	128	128	114	115
Median (Q1, Q3)	2890 (1775, 4815)	3280 (2220, 5350)	2305 (1570, 3785)	3120 (1930, 4345)	2485 (1520, 3760)	3080 (2010, 4220)

Idelalisib and the major oxidative metabolite GS-563117, plasma concentrations were comparable to each other at predose or 1.5 hours post-dose between Week 3 and Week 24. Mean trough concentrations of idelalisib were comparable to those observed in other studies (eg, monotherapy Study 101-02).

The PK of idelalisib and GS-563117, were characterised using post-hoc Bayesian forecasting utilising previous knowledge about the population PK. Resulting parameter estimates were similar to the results obtained from the population PK analysis in the original application.

The impact of various intrinsic factors on idelalisib and GS-563117 exposures was evaluated within the framework of the population PK analyses. The factors included age, gender, race, body weight, baseline creatinine clearance, AST, ALT, and background treatment. No significant effects of the evaluated factors on the PK of idealisib and GS-563117 were identified.

2.3.3. PK/PD modelling

Pharmacokinetic-Pharmacodynamic Relationship for Efficacy Parameters

Exposure efficacy analyses were conducted to assess the relationship between idelalisib exposures (derived from population PK modeling) and various efficacy endpoints, including change in tumour size (sum of the products of the greatest perpendicular diameters of index lesions), best overall response, duration of response (DOR), PFS, and lymph node response (LNR).

The analysis did not show a relationship between idelalisib exposure and various efficacy endpoints.

Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

Idelalisib and GS-563117 (primary metabolite) exposure-safety relationships were evaluated for subjects with CLL who received idelalisib 150 mg BID in combination with ofatumumab in Study GS-US-312-0119 and included laboratory abnormalities of AST and ALT and ≥ Grade 3 AEs including

neutropenia, diarrhoea, skin rash, infection, pneumonia, pneumonitis, and colitis. The analysis did not show a relationship between idelalisib/GS-563117 plasma exposures (AUC0-24h and Cmax) and analysed safety parameters.

2.3.4. Discussion on clinical pharmacology

Idelalisib exposures from subjects in Study GS-US-312 0119 with ofatumumab cotreatment were comparable to the exposures following idelalisib monotherapy (Study 101-02), indicating the lack of effect of ofatumumab coadministration on idelalisib.

Population PK modeling, assessment of the effect of intrinsic factors and exposure-response analyses (efficacy based on idelalisib exposures, safety based on idelalisib and GS-563117 exposures) were performed in subjects with relapsed/refractory CLL following administration of idelalisib 150 mg BID in combination with ofatumumab (Study GS-US-312-0119). The covariates evaluated had no clinically relevant effect on idelalisib plasma exposures. No relevant exposure-efficacy or exposure-safety relationships were noted. These results are consistent with the results from exposure-efficacy analyses reported previously for patients with CLL and indolent non-Hodgkin lymphoma (iNHL).

2.3.5. Conclusions on clinical pharmacology

The pharmacology studies for the combination of idelalisib with ofatumumab in CLL patients show consistent findings with data on exposure with idelalisib in combination with rituximab. The studies are considered adequate and acceptable to support the proposed indication.

2.4. Clinical efficacy

2.4.1. Main study

Study GS-US-312-0119: A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia

Methods

Study participants

Main inclusion criteria

1) Male or female ≥18 years of age

2) Diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and documented within medical records

3) CLL that warranted treatment (consistent with accepted IWCLL criteria for initiation of therapy.

4) Presence of radiographically measurable lymphadenopathy as assessed by computed tomography [CT] or magnetic resonance imaging [MRI])

5) Prior treatment for CLL comprising therapy with either of the following given alone or in combination: a) A purine analog (eg, fludarabine, pentostatin, cladribine) administered for ≥2 cycles of cytotoxic treatment, or b) Bendamustine administered for ≥2 cycles of treatment

6) Documentation of CLL progression < 24 months since the completion of the last prior therapy for CLL

7) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL > 6 weeks before randomization

8) 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, 2, 3, or 4 permitted])

9) Karnofsky performance score of ≥60

10) Specific Required baseline laboratory data (within 4 weeks prior to randomization). Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy could enroll.

11)For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and to 30 days from the last dose of study drug or 12 months from the last dose of ofatumumab (whichever is later)

12) For male subjects of child-bearing potential and having intercourse with females of child-bearing potential, willingness to use a protocol-recommended method of contraception from the randomisation visit (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug and to refrain from sperm donation from randomisation (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug

13) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL.

14) Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

15) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

Main exclusion criteria

1) Known histological transformation from CLL to an aggressive lymphoma (ie, Richter's transformation)

2) Known presence of intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have ≥5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥2 lineages of cytopenias due to myelodysplasia)

3) History of a non-CLL malignancy except adequately treated local or low-grade in complete remission for ≥2 years

4) Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for either idelalisib or ofatumumab

5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of initiation of randomisation (Visit 2)

6) Ongoing drug-induced liver injury, chronic active hepatitis C virus (HCV), chronic active HBV, alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension

7) Ongoing drug-induced pneumonitis

8) Ongoing inflammatory bowel disease

9) Ongoing alcohol or drug addiction

10) Pregnancy or breastfeeding

11) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation

12) Ongoing immunosuppressive therapy other than corticosteroids

13) In a subject with a history of prior ofatumumab therapy, the time from the last dose of ofatumumab to documented CLL progression was < 6 months

14) History of prior therapy with any inhibitor of serine/threonine protein kinase (Akt), Bruton tyrosine kinase, Janus kinase, mammalian target of rapamycin, PI3K (including idelalisib), or spleen tyrosine kinase

15) Prior participation in an idelalisib clinical study

16) Concurrent participation in another therapeutic clinical study

17) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results

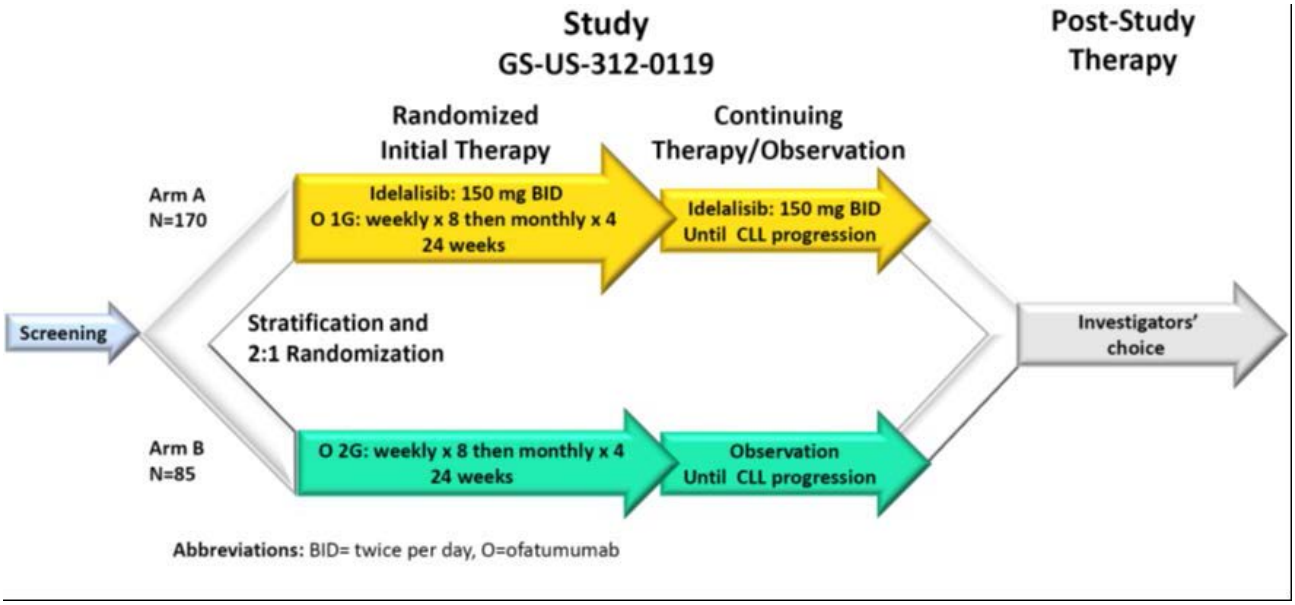
Treatments

Subjects were randomised with a 2:1 ratio into 1 of 2 treatment groups: Group A: idelalisib + ofatumumab and Group B: ofatumumab alone.

Before administration of ofatumumab, subjects were premedicated to reduce the incidence and severity of infusion reactions. In Group A, idelalisib was administered together with the premedication approximately 30 to 60 minutes before the ofatumumab infusions. For both treatments the first infusion of ofatumumab was administered at a dose of 300 mg. At each of Visits 3 through 13, subjects on both groups were given the recommended premedications, and ofatumumab was infused at a dose of 1000 mg (Group A) or 2000 mg (Group B).

Idelalisib was taken orally, twice daily, continuously. Tablets of 150-mg were used for initial therapy; the 100-mg tablets were provided for use by those subjects who required a dose reduction.

Figure 1: Study GS-US-312-0119 Design



Objectives

Primary objective

The primary objective of this study was to evaluate the effect of the addition of idelalisib to ofatumumab on Progression Free Survival (PFS) in subjects with previously treated CLL.

Secondary objectives

The secondary objectives were:

- To evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control
- To evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control for subjects with 17p deletion and/or TP53 mutation
- To assess the effect of the addition of idelalisib to ofatumumab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status
- To assess the effects of the addition of idelalisib to ofatumumab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib
- To characterize the effect of ofatumumab on idelalisib exposure through the evaluation of idelalisib plasma concentrations over time
- To describe the safety profile observed with the addition of idelalisib to ofatumumab
- To estimate health resource utilization associated with the addition of idelalisib to ofatumumab

Outcomes/endpoints

The primary endpoint for this study was PFS, defined as the interval from randomisation 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. The determination of CLL response and progression was based on scheduled imaging assessment, either CT

or MRI, utilizing standardized IWCLL criteria[1]. The occurrence of any of the following events indicated definitive PD:

- Evidence of any new disease:
    - A new node that measures >1.5 cm in any diameter
    - A new node that measures >1.0 cm to ≤ 1.5 cm in the LD and >1.0 cm in the LPD
    - New splenomegaly or recurrent splenomegaly (in a subject for whom spleen size had normalized) with a splenic LVD that now measures >2 cm larger than the cut-off value for the normal splenic LVD
    - New hepatomegaly or recurrent hepatomegaly (in a subject for whom liver size had normalized) with an hepatic LVD that now measures >2 cm larger than the cut-off value for the normal hepatic LVD
    - New non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)
- Evidence of worsening of index lesions, spleen or liver, or non-index disease:
    - Increase from the nadir by ≥50% in the SPD of index lesions
    - Evidence of worsening of individual index lymph nodes or nodal masses:
        - Increase from the nadir by ≥50% in the PPD for any individual node if the node now has a LD of >1.5 cm and there is an absolute change from the nadir of ≥0.5 cm in the LD or LPD and to ≥2.0 cm in absolute dimension.
        - Increase from the nadir by ≥50% in the LD for any individual node if the node now has a LD of >1.5 cm and there is an absolute change from the nadir of ≥0.5 cm in the LD
        - Increase from the nadir by ≥50% in the LPD for any individual node if the node now has a LPD of >1.5 cm and there is an absolute change from the nadir of ≥0.5 cm in the LPD
        - If a lesion had been classified as a small lymph node, there is an additional requirement that the lesion has an LD of >1.0 cm and an LPD of >1.0 cm.
    - In a subject with enlargement of the spleen at splenic nadir, there is an increase by ≥50% from the nadir value (minimum 2-cm increase) in the nadir enlargement of the LVD and the splenic LVD now measures >2 cm larger than the cut-off value for the normal splenic LVD
    - In a subject with enlargement of the liver at hepatic nadir, there is an increase by ≥50% from the nadir value (minimum 2-cm increase) in the nadir enlargement of the LVD with an hepatic LVD that now measures >2 cm larger than the cut-off value for the normal hepatic LVD
    - Unequivocal increase in the size of non-index disease (eg, effusions, ascites, or other organ abnormalities related to CLL)
    - Transformation to a more aggressive histology (eg, Richter syndrome) as established by lymph node biopsy

[1] Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood 2008;111 (12):5446-56.

- Decrease in platelet count or hemoglobin that is attributable to CLL, is not attributable to an autoimmune phenomenon, and is confirmed by bone marrow biopsy showing an infiltrate of clonal CLL cells
    - The current platelet count is <100 x 10^9/L and there has been a decrease by >50% from the highest on-study platelet count
    - The current hemoglobin is <110 g/L (11.0 g/dL) and there has been a decrease by >20 g/L (2 g/dL) from the highest on-study hemoglobin

Secondary efficacy endpoints were the following:

- Overall response rate (ORR) defined as the proportion of subjects who achieved a CR or PR and maintained their response for at least 8 weeks (with 1 week window).
- Lymph Node Response Rate (LNR) defined as the proportion of subjects who achieved a ≥ 50% decrease from baseline in the SPD of index lesions per IRC assessments.
- Overall Survival (OS) defined as the interval from randomisation to death from any cause during the study
- PFS in the subgroup of 17p deleted and/or TP53 mutated subjects – defined as the interval from randomisation to the earlier of the first documentation of definitive disease progression or death from any cause for 17p deleted and/or TP53 mutated subjects as collected in eCRF.
- Complete Response (CR) rate – defined as the proportion of subjects who achieved a CR and maintained their response for at least 8 weeks (with 1 week window).

Exploratory endpoints were as follows:

- Time to response (TTR) – defined as the interval from randomization to the first documentation of confirmed CR or PR for subjects who responded with confirmed CR or PR.
- Duration of response (DOR) – defined as the interval from the first documentation of confirmed CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause for subjects who responded with confirmed CR or PR.
- Percent change in lymph node area – defined as the percent change from baseline in the SPD of index lymph nodes.
- Splenomegaly response rate – defined as the proportion of subjects with a 50% decrease from baseline in the enlargement of the spleen in its LVD or to ≤ 12 cm by imaging.
- Hepatomegaly response rate – defined as the proportion of subjects with a 50% decrease from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging.
- ALC response rate – defined as the proportion of subjects with baseline lymphocytosis (ALC ≥ 4 × 109/L) who achieved an on-study ALC < 4 × 109/L or demonstrated a ≥ 50% decrease in ALC from baseline.
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count < 100 × 10^9/L) who achieved an on-study platelet count ≥ 100 × 10^9/L or demonstrated a ≥ 50% increase in platelet count from baseline without need for supportive care (eg, transfusion). Platelet values within 4 weeks postbaseline and 8 days after platelet transfusion and 4 weeks after thrombopoietic agents were excluded from the platelet response rate evaluation.
- Hemoglobin response rate – defined as the proportion of subjects with baseline anemia (hemoglobin < 110 g/L [11.0 g/dL]) who achieved an on-study hemoglobin ≥ 110 g/L (11.0 g/dL)

or demonstrated a ≥ 50% increase in hemoglobin from baseline without supportive care (eg, red blood cell transfusions). Hemoglobin values within 4 weeks postbaseline and 4 weeks post-red cell transfusion or erythropoietic stimulating agents (ESA) were excluded from the hemoglobin response rate evaluation.

- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] ≤ 1.5×10^9/L) who achieved an ANC > 1.5×10^9/L or demonstrated a ≥ 50% increase in ANC from baseline without need for exogenous growth factors. ANC values within 4 weeks postbaseline, 2 weeks after G-CSF or other growth factors and 4 weeks after Neulasta were excluded from the neutrophil response rate evaluation.
- Change from baseline in HRQL as reported by subjects using the FACT-Leu questionnaire.
- Changes in performance status as documented using the Karnofsky performance criteria.
- Change from baseline in overall health and single-item dimension scores as assessed using the EQ-5D questionnaire.

Sample size

Based on data from the Phase 2 pivotal study of ofatumumab and considering the population of subjects to be enrolled in this study, it was assumed that administration of ofatumumab to subjects with previously treated CLL in the ofatumumab single-agent group of this study would result in a median PFS of approximately 8 months.

An improvement in median PFS from 8 months to 14 months due to the addition of idelalisib to ofatumumab in Group A of the study corresponded to a benefit ratio of 1.75 (hazard ratio [HR]: 0.57).

It was assumed that PFS times were exponentially distributed in each of the 2 groups. With a HR equal to 1 under the null hypothesis of no difference between the 2 treatment groups and a HR of 0.57 under the alternative hypothesis of superiority of the idelalisib–containing combination, 129 events (definitive CLL progressions or deaths) were required to achieve a power of approximately 0.85 based on a log-rank test with a 2-sided significance level of 0.05. Further assumptions included a planned accrual period of 12 months (with approximately half of the subjects enrolled during the initial 60% of the accrual period, and the remaining half of the subjects enrolled during the last 40% of the accrual period); a minimum follow-up period of 12 months; and an expectation that 10% of subjects would be lost to follow-up (5% during the accrual period and 5% during the follow-up period).

Given these assumptions, in order to ensure that the primary analysis on PFS would be performed before or at the planned minimum 12-month follow-up period, approximately 170 subjects were to be enrolled into the idelalisib + ofatumumab group and approximately 85 subjects were to be enrolled into the ofatumumab single-agent group. Based on this, the expected number of events would be achieved by the end of the planned minimum 12-month follow-up period. It was expected that there would be approximately 65 deaths at the time of final analysis. This provided approximately 85% power to detect a HR of 0.45 for OS based on a log-rank test at 2-sided alpha level of 0.03.

Randomisation

Subjects were randomized in a 2:1 ratio to either of the following treatment assignments:

Group A: idelalisib + ofatumumab (1000-mg dosing regimen)

Group B: ofatumumab alone (2000-mg dosing regimen)

A fixed-block centralised randomisation allocated subjects within the 8 strata as defined by the intersection of the following 3 binary stratification factors:

- 17p deletion and/or TP53 mutation in CLL cells: either versus neither (or indeterminate)
- 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)

Blinding (masking)

This was an open-label study.

Statistical methods

The primary endpoint analysis served as the gatekeeper for the secondary endpoint analyses, ie, the primary efficacy hypothesis (the null hypothesis) was to be rejected at the 2-sided significance level before the efficacy hypotheses for the secondary efficacy endpoints could be evaluated. If the primary hypothesis was rejected at either an interim or final analysis, the 5 secondary endpoints were to be sequentially tested at the 2-sided significance level of 0.03 in the order listed above. The significance level was chosen in such a way that the overall Type I error rate of testing primary and secondary endpoints was preserved at the 2-sided significance level of 0.05. If a null hypothesis was not rejected, formal sequential testing was to be stopped and only nominal significance would be cited for the remaining secondary endpoints.

Two formal interim efficacy analyses were planned after approximately 50% and 75% of the PFS events had occurred.

Table 2: Expected Number of Events at Interim and Final Analyses and Significance Levels to Reject H0

Analyses	Expected Number of Events[a], n (%)		Significant Level to Reject H_0
Interim #1	65	(50%)	< 0.003
Interim #2	97	(75%)	< 0.018
Final	129	(100%)	< 0.044

a Definitive CLL progressions or deaths

By the date projected for the first interim analysis, when 50% of [the expected 129] PFS events were estimated to have occurred, the actual number of PFS events approached the number of PFS events targeted for the second interim (75% PFS events). The first interim analysis was conducted at this point at a significance level of 0.018, and a decision was made to continue the study until the final analysis. There was no second interim analysis. The primary efficacy analysis reported was the planned final analyses based on approximately 129 PFS events.

Descriptive statistics were provided for TTR. DOR was summarized using KM methods (medians, Q1, Q3, and corresponding 95% CIs) and a plot of the KM curves for DOR was provided by treatment group.

The best percent change in SPD from baseline during the study was summarised using descriptive statistics.

Differences between treatment groups for splenomegaly response rate, hepatomegaly response rate, ALC response rate, platelet response rate, hemoglobin response rate, and neutrophil response rate were compared using CMH Chi-square tests after adjusting for stratification factors. For all analyses, odds ratios and the corresponding 95% CIs were presented.

Results

Participant flow

Patient disposition is displayed in Table 3.

Table 3: Disposition of Subjects - Study GS-US-312-0119 (ITT analysis)

Subject Disposition[a]	Id + O (N = 174) n (%)	O (N = 87) n (%)
Randomized	174 (100.0)	87 (100.0)
Treated	173 (99.4)	86 (89.9)
Ongoing in Study	84 (48.3)	6 (6.9)
Met Primary Study Endpoint[a]	56 (32.2)	47 (54.0)
Disease Progression	34 (19.5)	41 (47.1)
Death	22 (12.6)	6 (6.9)
Discontinued Study[a]	34 (19.5)	34 (39.1)
Adverse Event[b]	2 (1.1)	3 (3.4)
Other	1 (0.6)	1 (1.1)
Physician Decision	19 (10.0)	16 (18.4)
Withdrawal by Subject	12 (6.9)	14 (16.1)

Id = idelalisib; O = ofatumumab; PD = progressive disease

a Reason for discontinuation as determined by investigator; includes subjects who were later determined to have PD by the IRC

b Permitted as a valid reason for study discontinuation only through Version 2 of the protocol.

Recruitment

The first subject was screened on 04 December 2012 and the last subject observation for the interim report was on 15 January 2015. The study was conducted in 81 sites in the United States, Canada, Belgium, Denmark, France, Ireland, Poland, Spain, Sweden, United Kingdom, and Australia.

Conduct of the study

The original protocol (Version 1.0) had 6 updates. The main changes were as follows:

In the 1st amendment (09-NOV-2012) a new section was added to differentiate discontinuation from study versus discontinuation of drug.

The 2nd amendment (13-OCT-2013) increased planned sample size to 255 and removed AEs as a reason for discontinuation from study.

The 5th amendment (26-SEP-2014) added the secondary objective to evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumor control for subjects with 17p deletion and/or TP53 mutation.

Protocol deviations

A list of the main protocol deviations are presented below. The most common type of major protocol deviation was stratification error. The primary type of stratification error was incorrect reporting of disease status (refractory vs relapsed) at enrollment. These errors were corrected during database cleaning, but after the subjects had already been assigned to treatment groups based on the stratum designated at enrollment. The primary efficacy analyses were performed by corrected stratum.

Table 4: Important Protocol Deviations Occurring in 5 or More Subjects - Study GS-US-312-0119 (ITT analysis)

Protocol Deviation, n (%)	Id + O (N = 174)	O (N = 87)
Number of Subjects with at Least 1 Important Protocol Deviation	68 (39.1)	34 (39.1)
Stratification error	38 (21.8)	24 (27.6)
Informed consent form	12 (6.9)	2 (2.3)
Safety reporting	5 (2.9)	4 (4.6)
Study procedure	6 (3.4)	2 (2.3)
Authorization, delegation, training	3 (1.7)	2 (2.3)
No purine analog/bendamustine	4 (2.3)	1 (1.1)

Id = idelalisib; O = ofatumumab

Table 5: Stratification errors - Study GS-US-312-0119

	Id + O (N = 174)		O (N = 87)	
Stratification Factor	Reported in the Clinical Database	Reported in IVRS	Reported in the Clinical Database	Reported in IVRS
17p deletion and/or p53 mutation				
Either	70	67	33	33
Neither	104	107	54	54
IGHV Mutation Status				
Mutated	37	40	19	20
Unmutated	137	134	68	67
Disease Status				
Refractory	82	73	47	36
Relapsed	92	101	40	51

Id = idelalisib; IGHV = immunoglobulin heavy chain variable region; O = ofatumumab

Baseline data

A summary of patient demographics and baseline characteristics for the ITT population are presented in the tables below.

Table 6: Demographic and Baseline Characteristics - Study GS-US-312-0119 (ITT Analysis Set)

Characteristic	Id + O (N = 174)	O (N = 87)	Total (N = 261)
Gender, n (%)			
Male	124 (71.3)	62 (71.3)	186 (71.3)
Female	50 (28.7)	25 (28.7)	75 (28.7)
Race, n (%)			
White	149 (85.6)	71 (81.6)	220 (84.3)
Black or African American	0	4 (4.6)	4 (1.5)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	1 (0.4)
Asian	2 (1.1)	0	2 (0.8)
Other	2 (1.1)	3 (3.4)	5 (1.9)
Not Permitted	20 (11.5)	9 (10.3)	29 (11.1)
Age (years)[a]			
N	174	87	261
Mean (StD)	67 (9.0)	67 (9.7)	67 (9.2)
95% CI	66, 68	65, 69	66, 68
Median	68	67	68
Q1, Q3	61, 74	62, 74	61, 74
Min, Max	40, 85	36, 84	36, 85
Age Group (years)			
< 65	67 (38.5)	27 (31.0)	94 (36.0)
≥ 65	107 (61.5)	60 (69.0)	167 (64.0)
BMI (kg/m^2)[b]			
N	169	86	255
Mean (StD)	26.8 (4.93)	26.7 (4.97)	26.8 (4.94)
95% CI	26.0, 27.5	25.7, 27.8	26.1, 27.4
Median	26.1	26.3	26.1
Q1, Q3	23.4, 29.2	22.8, 29.3	23.1, 29.3
Min, Max	17.3, 45.8	18.4, 41.8	17.3, 45.8
Splenomegaly	131 (75.3)	61 (70.1)	192 (73.6)
Hepatomegaly	90 (51.7)	49 (56.3)	139 (53.3)
Karnofsky Performance Status, n (%)			
60	6 (3.4)	3 (3.4)	9 (3.4)
70	27 (15.5)	14 (16.1)	41 (15.7)
80	56 (32.2)	34 (39.1)	90 (34.5)
90	59 (33.9)	27 (31.0)	86 (33.0)
100	26 (14.9)	9 (10.3)	35 (13.4)
Karnofsky Performance Status < 80, n (%)	33 (19.0)	17 (19.5)	50 (19.2)
Creatinine Clearance (mL/sec)			
N	171	84	NA
Mean (StD)	1.25 (0.441)	1.28 (0.437)	NA
95% CI	1.19, 1.32	1.19, 1.38	NA
Median	1.20	1.24	NA
Q1, Q3	0.95, 1.45	0.95, 1.53	NA
Min, Max	0.50, 2.70	0.53, 2.56	NA

BMI = body mass index; CI = confidence interval; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation

a Age (years) = (date of randomization – date of birth + 1) / 365.25

b BMI (kg/m^2) = weight / $height^2$

Table 7: CLL Disease History - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)	Total (N = 261)
Time Since Diagnosis (months)[a]			
N	173	86	259
Mean (StD)	101.0 (60.20)	94.3 (52.51)	98.8 (57.75)
Median	93.0	91.7	92.8
Q1, Q3	59.8, 131.2	56.3, 126.9	57.1, 129.2
Min, Max	7.8, 351.8	6.7, 268.5	6.7, 351.8
Rai Stage at Screening, n (%)			
0	3 (1.7)	2 (2.3)	5 (1.9)
I	24 (13.8)	11 (12.6)	35 (13.4)
II	26 (14.9)	21 (24.1)	47 (18.0)
III	24 (13.8)	10 (11.5)	34 (13.0)
IV	93 (53.4)	39 (44.8)	132 (50.6)
Not Available/Missing	4 (2.3)	4 (4.6)	8 (3.1)
Binet Stage at Screening, n (%)			
A	11 (6.3)	6 (6.9)	17 (6.5)
B	51 (29.3)	29 (33.3)	80 (30.7)
C	107 (61.5)	45 (51.7)	152 (58.2)
Not Available/Missing	5 (2.9)	7 (8.0)	12 (4.6)

CI = confidence interval; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation

a Time Since Diagnosis is calculated as (date of randomization – date of diagnosis) / 30.4375.

Table 8: Subject Distribution by Stratification Factors - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)	Total (N = 261)
17p deletion and/or TP53 mutation			
Either	70 (40.2)	33 (37.9)	103 (39.5)
Neither	104 (59.8)	54 (62.1)	158 (60.5)
IGHV mutation status			
Mutated	37 (21.3)	19 (21.8)	56 (21.5)
Unmutated	137 (78.7)	68 (78.2)	205 (78.5)
Disease status			
Refractory	82 (47.1)	47 (54.0)	129 (49.4)
Relapsed	92 (52.9)	40 (46.0)	132 (50.6)
17p deletion and/or TP53 mutation, and IGHV mutated	11 (6.3)	5 (5.7)	16 (6.1)
Refractory disease	8 (4.6)	2 (2.3)	10 (3.8)
Relapsed disease	3 (1.7)	3 (3.4)	6 (2.3)
17p deletion and/or TP53 mutation, and IGHV unmutated	59 (33.9)	28 (32.2)	87 (33.3)
Refractory disease	30 (17.2)	17 (19.5)	47 (18.0)
Relapsed disease	29 (16.7)	11 (12.6)	40 (15.3)
Neither 17p deletion nor TP53 mutation, and IGHV mutated	26 (14.9)	14 (16.1)	40 (15.3)
Refractory disease	11 (6.3)	4 (4.6)	15 (5.7)
Relapsed disease	15 (8.6)	10 (11.5)	25 (9.6)
Neither 17p deletion nor TP53 mutation, and IGHV unmutated	78 (44.8)	40 (46.0)	118 (45.2)
Refractory disease	33 (19.0)	24 (27.6)	57 (21.8)
Relapsed disease	45 (25.9)	16 (18.4)	61 (23.4)

Id = idelalisib; IGHV = immunoglobulin heavy chain variable region; O = ofatumumab

Table 9: Summary of Baseline Haematology and Comorbidities - Study GS-US-312-0119 (ITT Analysis)

	Id + O (N = 174)	O (N = 87)	Total (N = 261)
Platelet Count < 100×10^9/L, n (%)	97 (56.1)	46 (53.5)	143 (55.2)
Hemoglobin < 11.0 g/dL, n (%)	77 (44.3)	45 (52.3)	122 (46.9)
Hemoglobin < 12.5 g/dL, n (%)	130 (74.7)	61 (70.9)	191 (73.5)
Absolute Neutrophil Count < 1.5×10^9/L, n (%)	35 (20.1)	23 (27.1)	58 (22.4)
Median (Q1, Q3) CIRS Score	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)
Total CIRS Score > 6, n (%)	54 (31.0)	23 (26.4)	77 (29.5)

CIRS = Cumulative Illness Rating Scale; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile

Table 10: Prior Therapy- Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)	Total (N = 261)
Median Time Since Last Prior Regimen, Months (Q1, Q3)[a]	9.3 (5.1, 20.3)	9.3 (3.6, 17.9)	9.3 (4.3, 19.4)
Number of Prior Regimens			
N	174	87	261
Mean (StD)	3.2 (2.18)	3.5 (2.08)	3.3 (2.15)
Median	3.0	3.0	3.0
Q1, Q3	2.0, 4.0	2.0, 5.0	2.0, 4.0
Min, Max	1.0, 11.0	1.0, 11.0	1.0, 11.0
Most Common Last Regimens Prior to Study Entry, n (%)[b]			
BR	51 (31.0)	21 (24.1)	75 (28.7)
FCR	38 (21.8)	18 (20.7)	56 (21.5)
FR	9 (5.2)	5 (5.7)	14 (5.4)
R	8 (4.6)	5 (5.7)	13 (5.0)

BR = bendamustine + rituximab; FCR = fludarabine + cyclophosphamide + rituximab; FR = fludarabine + rituximab; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; R = rituximab; StD = standard deviation

a Time since completion of last regimen (months) = (date of randomization – date of completion of last regimen) / 30.4375

b Regimens received by ≥ 5% of subjects in either treatment group.

Numbers analysed

The Intent-to Treat (ITT) Analysis Set included data from all subjects who were randomised regardless of whether subjects received any study drugs, or received a different regimen from that to which they were randomised. Treatment assignment was designated according to randomisation. This analysis set was used in the analyses of subject characteristics, PFS, ORR, OS, LNR, CR rate, and health outcomes variables. The analysis of PFS based on the ITT Analysis Set was considered the primary analysis of the study.

A Safety Analysis Set included data from subjects who received ≥1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

The PK Analysis Set included data from subjects in the Safety Analysis Set who had the necessary baseline and on-study measurements to provide interpretable PK results.

Table 11: Analysis Sets - Study GS-US-312-0119

	Id + O (N = 174)	O (N = 87)	Total (N = 261)
ITT Analysis Set, n (%)	174 (100.0)	87 (100.0)	261 (100.0)
Safety Analysis Set, n (%)	173 (99.4)	86 (98.9)	259 (99.2)
PP Analysis Set, n (%)	163 (93.7)	84 (96.6)	247 (94.6)

Id = idelalisib; ITT = Intent-to-Treat; O = ofatumumab; PP = Per Protocol

Outcomes and estimation

Primary Efficacy Endpoint - PFS

Analysis of PFS as assessed by the IRC based on the ITT Analysis Set and stratified by 17p deletion and/or TP53 mutation status, IGHV mutation status, and disease status is summarised in the table and figures below.

Table 12: Progression Free Survival by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects with Events	76 (43.7)	54 (62.1)
Disease Progression	54 (31.0)	48 (55.2)
Death	22 (12.6)	6 (6.9)
Number (%) of Subjects Censored	98 (56.3)	33 (37.9)
Ongoing	75 (43.1)	4 (4.6)
Discontinued Study without Event	21 (12.1)	29 (33.3)
Missed ≥ 2 Consecutive Tumor Measurements	2 (1.1)	0
KM Estimate of PFS (Months)[a]		
Q1 (95% CI)	9.0 (7.5, 10.8)	3.5 (1.8, 5.3)
Median (95% CI)	16.3 (13.6, 17.8)	8.0 (5.7, 8.2)
Q3 (95% CI)	NR (17.8, NR)	9.2 (8.2, 16.4)
Adjusted HR (95% CI)[b]	0.27 (0.19, 0.39)	
P-value[c]	< 0.0001	

Figure 2: KM Curve of PFS by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

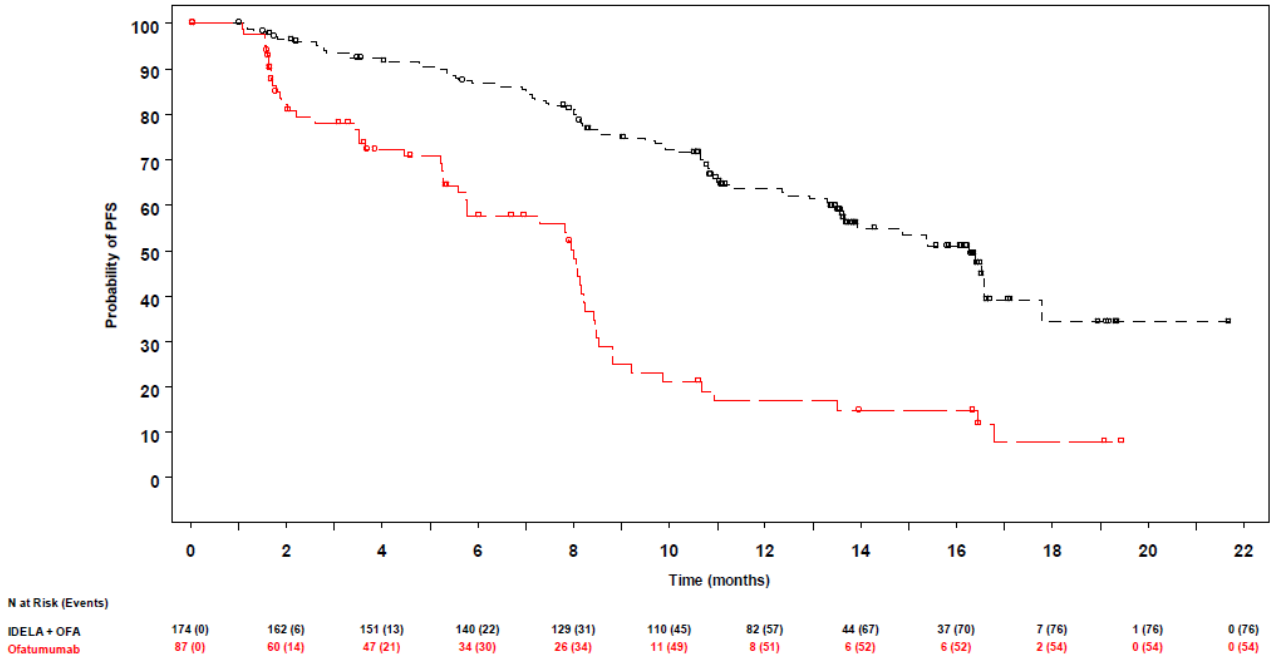
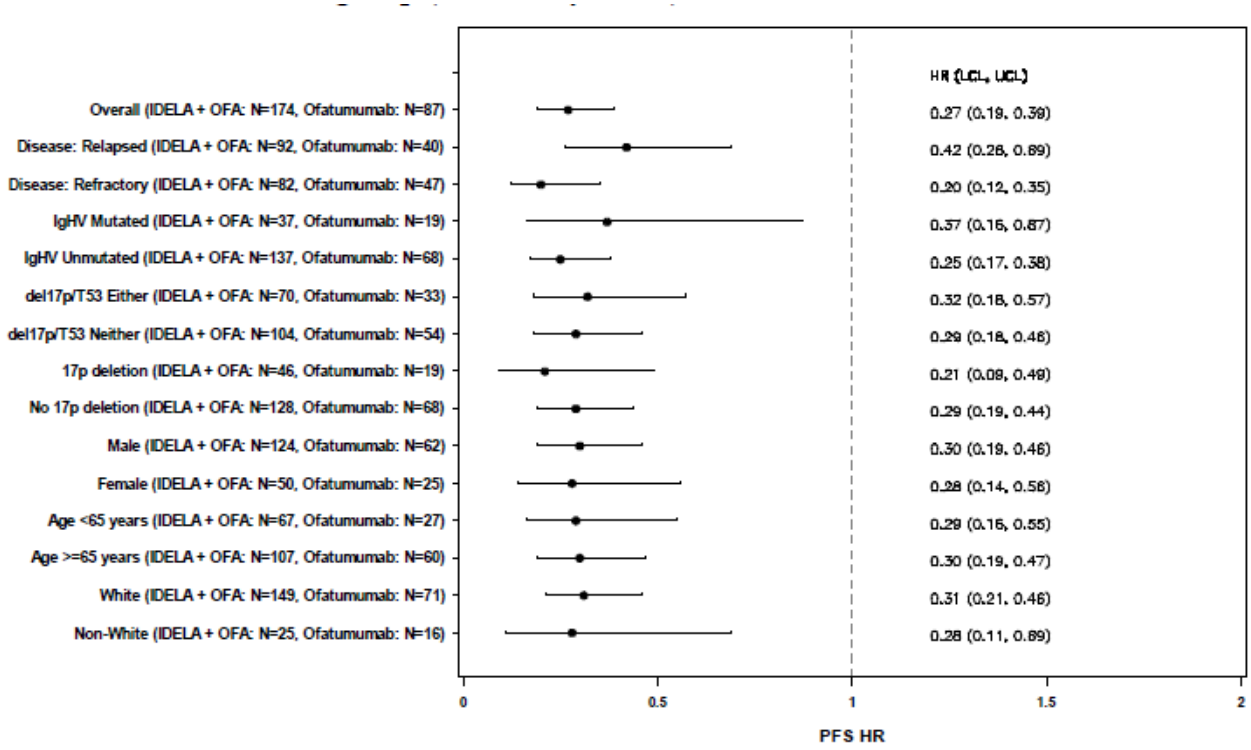


Figure 3: Forest Plot of PFS per IRC Assessment by Subgroup - Study GS-US-312-0119 (ITT Analysis Set)



IgHV = immunoglobin heavy chain variable region; OFA = ofatumumab; PFS = progression-free survival

Key secondary endpoints

The secondary efficacy endpoints were ORR, LNR rate OS, PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation and CR rate. The data are presented in the following tables.

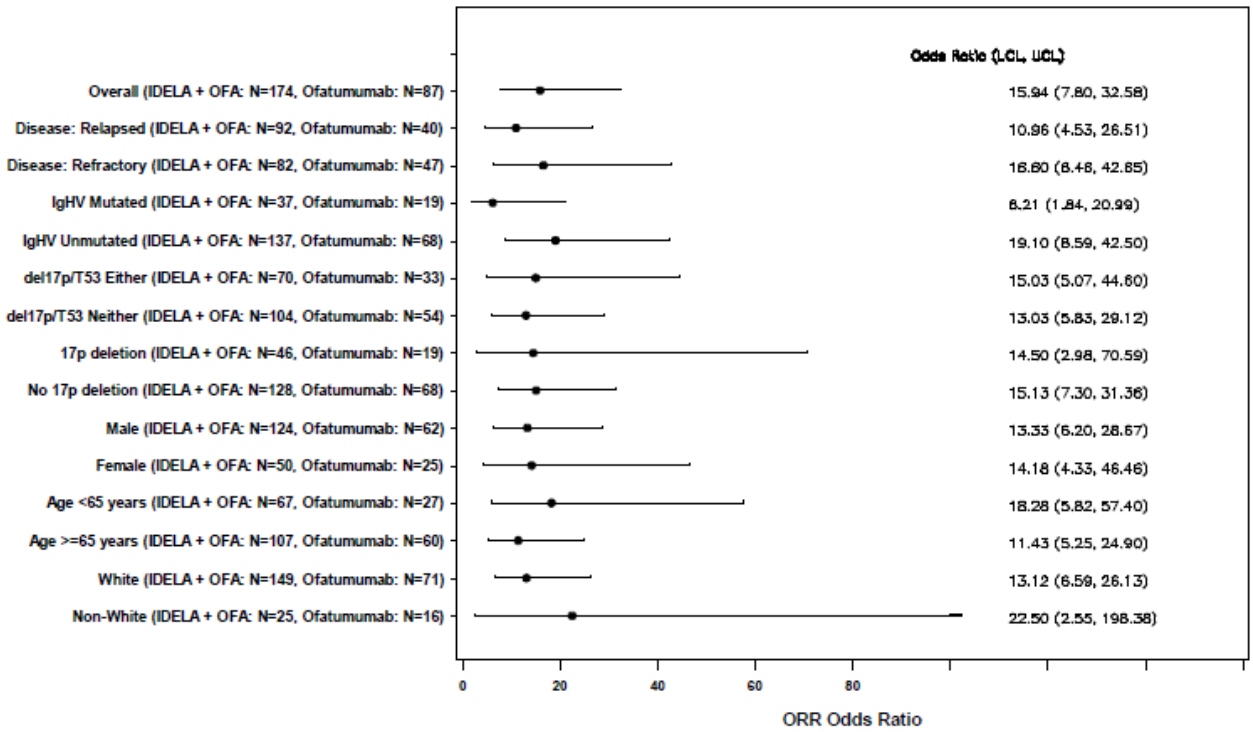
- **Overall response rate**

Table 13: ORR by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N =174)	O (N = 87)
Best Overall Response, n (%)		
Complete Response (CR)	1 (0.6)	0
Partial Response (PR)	130 (74.7)	16 (18.4)
Stable Disease (SD)	31 (17.8)	51 (58.6)
Progressive Disease (PD)	1 (0.6)	13 (14.9)
Not Evaluable (NE)	11 (6.3)	7 (8.0)
No Disease	0	0
ORR[a]	131 (75.3)	16 (18.4)
95% CI[b]	68.2, 81.5	10.9, 28.1
Odds Ratio for Overall Response[c]	15.94	
95% CI for Odds Ratio	7.8, 32.58	
P-value	< 0.0001	

CI = confidence interval; Id = idelalisib; IRC = Independent Review Committee; O = ofatumumab; ORR = overall response rate
Subjects with CR or PR who maintain the response for at least 8 weeks (with 1 with interval) are defined to have confirmed

Table 14: Forest Plot of ORR per IRC Assessment by Subgroup - Study GS-US-312-0119 (ITT Analysis Set)



IgHV = immunoglobin heavy chain variable region; OFA = ofatumumab; PFS = progression-free survival

- **Lymph node response rate**

Table 15: Lymph Node Response Rate - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)
LNR Rate[a]	153/164 (93.3)	4/81 (4.9)
95% CI for LNR Rate[b]	88.3, 96.6	1.4, 12.2
Odds Ratio[c]	486.96	
95% CI for Odds Ratio	97.91, 2421.85	
P-value	< 0.0001	

CI = confidence interval; Id = idelalisib; LNR = lymph node response; O = ofatumumab

a LNR rate was defined as the percentage of subjects who achieved a ≥ 50% decreased from baseline in the SPD of index lymph nodes.

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

c Odds ratio, 95% CI, and p-value was calculated from the Cochran-Mantel-Haenszel Chi-square test stratified by stratification factors.

Table 16: Lymph Node Response (Odds Ratio) for Predefined Subgroups - Study GS-US-312-0119 (ITT Analysis Set)

Subgroup Factor	Odds Ratio (95% CI)[b]
Either 17p deletion and/or TP53 Mutation Present	284.67 (32.71, 2477.69)
Neither 17p deletion nor TP53 Mutation Present	300.53 (68.91, 1310.66)
Mutated IGHV	140.25 (18.14, 1084.49)
Unmutated IGHV	400 (83.79, 1909.63)
17p deletion	NE (NE, NE)
No 17p deletion	248.36 (69.94, 881.9)
Refractory	528 (61.51, 4532.66)
Relapsed	178.2 (40.26, 788.7)
Males	204.43 (57.31, 729.17)
Females	NE (NE, NE)
Age < 65 years	195.43 (22.79 – 1675.85)
Age ≥ 65 years	424 (91.44, 1966.08)
Whites	229.06 (67.91, 772.56)
Non-Whites	NE (NE, NE)

CI = confidence interval; IGHV = immunoglobulin heavy chain variable region; NE = Not estimable
Analysis only included subjects in the ITT Analysis Set that 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.

b Odd ratio and 95% CI are calculated without any adjustment.

- **Overall Survival**

The primary OS analysis was performed using the ITT Analysis Set (according to the original randomisation) which included all available survival information from Study GS-US-312-0119 (including data in long-term follow-up), up to the data cutoff date of 15 January 2015. Data with a cutoff date of 01 September 2015, representing approximately 7.5 months of additional follow-up for survival was also submitted. A summary of OS, both from the primary analysis and based on the data cutoff of 01 September 2015, is presented in the table and figures below.

Table 17: Overall Survival - Study GS-US-312-0119 (ITT Analysis Set)

	Primary Efficacy Analysis (Data Cutoff 15 Jan 2015)		Updated Analysis (Data Cutoff 01 Sep 2015)	
	Id + O (N = 174)	O (N = 87)	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects with Events	42 (24.1)	22 (25.3)	55 (31.6)	29 (33.3)
Death	42 (24.1)[a]	22 (25.3)	55 (31.6)	29 (33.3)
Number (%) of Subjects Censored	132 (75.9)	65 (74.7)	119 (68.4)	58 (66.7)
Ongoing	84 (48.3)	6 (6.9)	51 (29.3)	1 (1.1)
Discontinued Study	48 (27.6)	59 (67.8)	68 (39.1)	57 (65.5)
KM Estimate of OS (Months)[b]				
Q1 (95% CI)	15.8 (11.4, 20.9)	13 (6.0, 19.4)	18.2 (12.3, 22.7)	12.7 (6.0, 17.6)
Median (95% CI)	20.9 (20.9, NR)	19.4 (16.9, NR)	NR (25.8, NR)	NR (21.7, NR)
Q3 (95% CI)	NR (20.9, NR)	NR (19.4, NR)	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI)	0.74 (0.44, 1.25)		0.75 (0.48, 1.18)	
P-value[c]	0.27		0.27	

CI = confidence interval; HR = hazard ratio; Id = idelalisib; KM = Kaplan Meier; NR = not reached; O = ofatumumab; OS = overall survival; Q1 = first quartile; Q3 = third quartile

a One subject who died in the idelalisib + ofatumumab group did not receive treatment and therefore is not included in safety analyses.

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

c P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation, and disease status).

Source: GS-US-312-0119 Interim (Primary Analysis) CSR Table 9-5; Table CHMP.17

Figure 4: KM Curve of Overall Survival - Study GS-US-312-0119 (ITT Analysis Set)

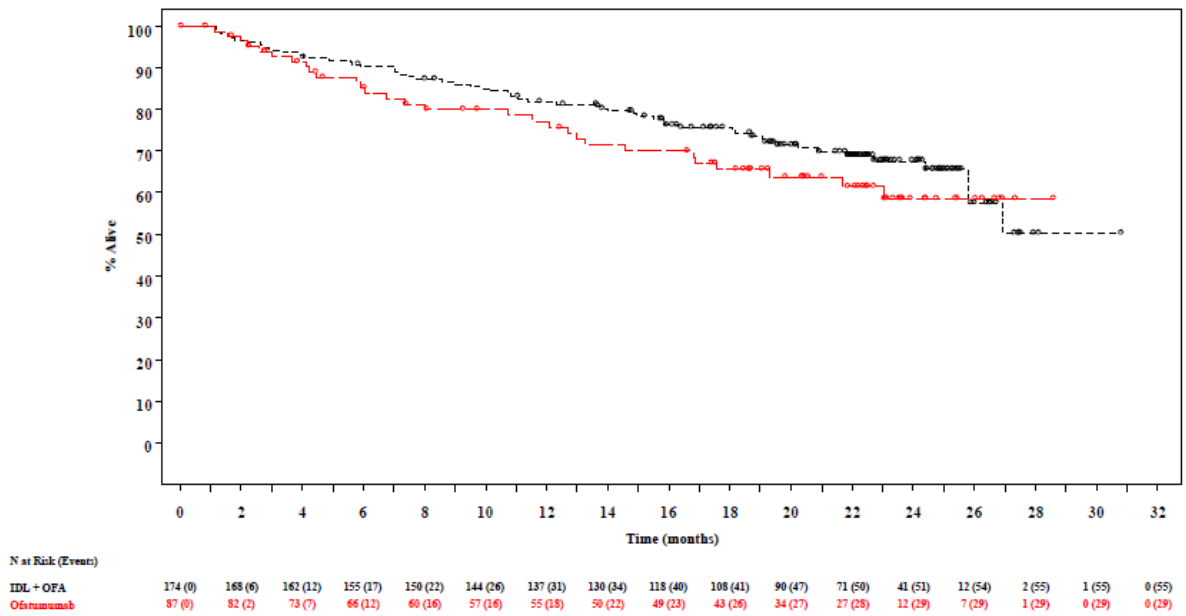


Table 18: Overall Survival HRs for predefined subgroups – GS-US-312-0119 (ITT Analysis Set)

Subgroup Factor	Adjusted HR (95% CI)[a]
Either 17p deletion and/or TP53 Mutation Present	0.56 (0.27, 1.16)
Neither 17p deletion nor TP53 Mutation Present	0.94 (0.45, 2)
Mutated IGHV	1.26 (0.3, 5.24)
Unmutated IGHV	0.72 (0.41, 1.25)
17p deletion	0.62 (0.25, 1.54)
No 17p deletion	0.75 (0.39, 1.42)
Refractory	0.76 (0.38, 1.51)
Relapsed	0.74 (0.33, 1.66)
Males	0.85 (0.46, 1.58)
Females	0.77 (0.28, 2.12)
Age < 65 years	0.41 (0.15, 1.09)
Age ≥ 65 years	1.05 (0.57, 1.94)
Whites	0.87 (0.47, 1.6)
Non-Whites	0.5 (0.18, 1.45)

CI = confidence interval; HR = hazard ratio; IGHV = immunoglobulin heavy chain variable region; NR = not reached

a Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model without any adjustments.

- **PFS in the Subgroup of Subjects with 17p Deletion and/or TP53 Mutation**

Table 19: PFS for Subjects with 17p Deletion and/or TP53 Mutation by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

	Deletion/Mutation: Either		Deletion/Mutation: Neither	
	Id + O N = 70	O N = 33	Id + O N = 104	O N = 54
Number (%) of Subjects with Events	35 (50.0)	20 (60.6)	41 (39.4)	34 (63.0)
Disease Progression	25 (35.7)	16 (48.5)	29 (27.9)	32 (59.3)
Death	10 (14.3)	4 (12.1)	12 (11.5)	2 (3.7)
Number (%) of Subjects Censored	35 (50.0)	13 (39.4)	63 (60.6)	20 (37.0)
Ongoing	27 (38.6)	1 (3.0)	48 (46.2)	3 (5.6)
Discontinued Study without Event	6 (8.6)	12 (36.4)	15 (14.4)	17 (31.5)
Missed ≥ 2 Consecutive Tumor Measurements	2 (2.9)	0	0	0
KM Estimate of PFS (Months)[a]				
Q1 (95% CI)	8.6 (5.4, 11)	2.6 (1.7, 5.3)	9.5 (7.4, 11.4)	3.6 (1.7, 7.3)
Median (95% CI)	13.7 (11, 17.8)	5.8 (4.5, 8.4)	16.4 (13.9, NR)	8.1 (5.6, 8.5)
Q3 (95% CI)	17.8 (16.5, NR)	8.5 (8, NR)	NR (NR, NR)	9.9 (8.2, 16.4)
Unadjusted HR (95% CI)[b]	0.32 (0.18, 0.57)		0.29 (0.18, 0.46)	
P-value	< 0.0001		NA	

CI = confidence interval; HR = hazard ratio; Id = idelalisib; NR = not reached; O = ofatumumab; 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 without any adjustment

Source: Section 15.1, Tables 2.1.1.1 and 2.1.1.2

Figure 5: KM Curve of PFS in Subjects with 17p Deletion and/or TP53 Mutation – Either - Study GS-US-312-0119 (ITT Analysis Set)

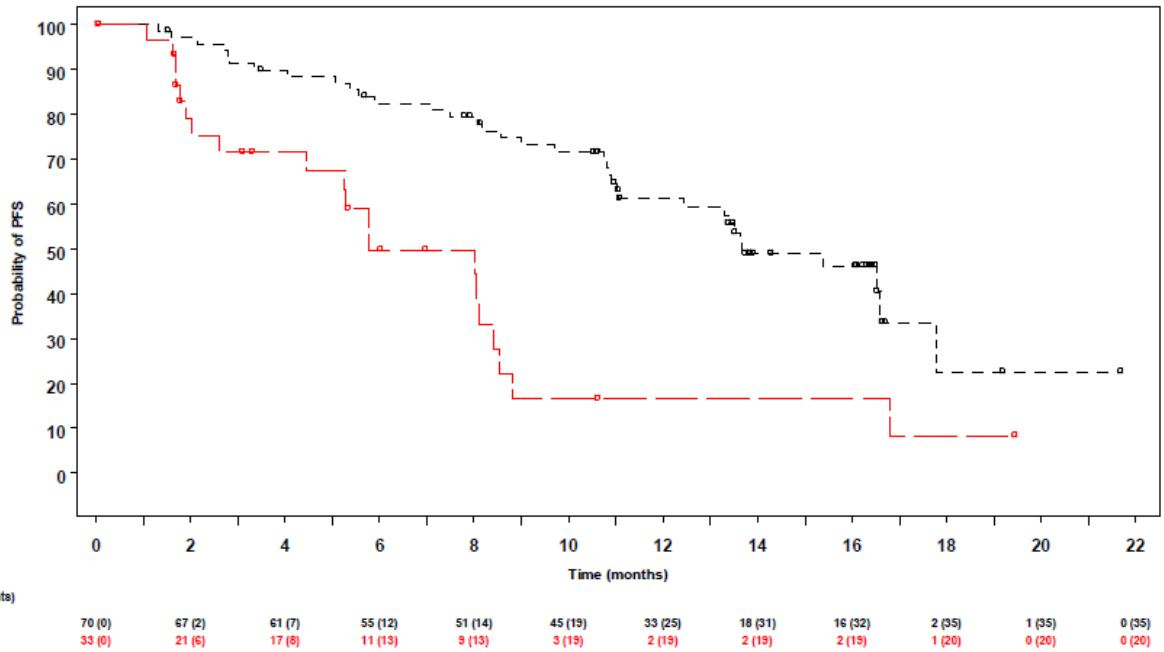
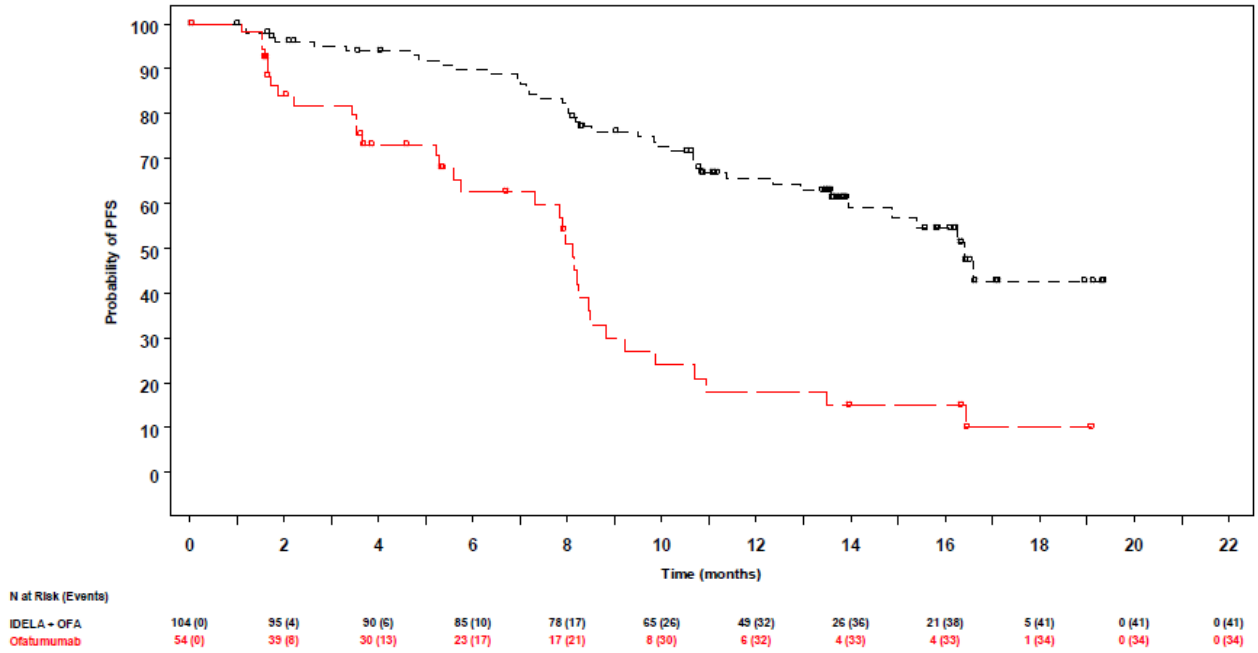


Figure 6: KM Curve of PFS in Subjects with 17p Deletion and/or TP53 Mutation – Neither - Study GS-US-312-0119 (ITT Analysis Set)



The unadjusted hazard ratio of PFS for subjects with 17p deletion and/or TP53 mutation was 0.32 (p < 0.0001) and for subjects with neither was 0.29 (p-value not calculated for this subgroup) (Table 19).

Table 20: Efficacy Results by 17p Deletion and/or TP53 Mutation Status - Study GS-US-312-0119

Endpoint (Measure)	Subjects with 17p Deletion and/or TP53 Mutation		Subjects with Neither 17p Deletion nor TP53 Mutation	
	Id + O (N = 70)	O (N = 33)	Id + O (N = 104)	O (N = 54)
PFS, HR (95% CI)	0.32 (0.18, 0.57), p < 0.0001		0.29 (0.18, 0.46), NA	
ORR, odds ratio (95% CI)	15.03 (5.07, 44.6)		13.03 (5.83, 29.12)	
LNR rate, odds ratio (95% CI)	284.67 (32.71, 2477.69), p < 0.0001		300.53 (68.91, 1310.66), p < 0.0001	
OS (HR)	0.56 (0.27, 1.16), p = 0.1152		0.94 (0.45, 2), p = 0.8809	
DOR, median (95% CI) months	14 (9.3, NR)	6.5 (4.7, NR)	14.9 (12.9, NR)	6.7 (5.4, 15.0)

- **Complete Response Rate**

As there was only 1 CR on study, this analysis was not performed.

Exploratory endpoints

The results for the exploratory analyses for TTR, DOR, best percent change in sum of the product of greatest perpendicular diameter (SPD), splenomegaly, hepatomegaly response rates, ALC, platelet, haemoglobin, ANC response rates and Health-Related Quality of Life measures are presented below.

- **Time to Response**

Table 21: Time to Response by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

Time to Response (Months)[a]	Id + O (N = 174)	O (N = 87)
N	131	16
Mean (StD)	2.8 (2.05)	2.6 (1.38)
Median	1.7	1.7
Q1, Q3	1.6, 3.4	1.5, 3.5
Min, Max	1.4, 10.9	1.4, 5.4

Id = idelalisib; IRC = independent review committee; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation
Analysis included only subjects in the ITT Analysis Set who achieved CR or PR.
a TTR (months) = (date of first PR/CR – date of randomization + 1) / 30.4375.
Source: Section 15.1, Table 2.6.1

- **Duration of Response**

Table 22: Duration of Response by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects with CR or PR	131 (75.3%)	16 (18.4%)
Number (%) of Subjects with Events	47 (35.9%)	10 (62.5%)
Disease Progression	39 (29.8%)	10 (62.5%)
Death	8 (6.1%)	0
Number (%) of Subjects Censored	84 (64.1%)	6 (37.5%)
Ongoing	73 (55.7%)	3 (18.8%)
Discontinued Study	11 (8.4%)	3 (18.8%)
KM Estimate of DOR (Months)[a]		
Q1 (95% CI)	9.2 (8.0, 11.4)	6.4 (4.7, 6.5)
Median (95% CI)	14.9 (12.9, NR)	6.7 (5.6, 15.0)
Q3 (95% CI)	NR (16.3, NR)	15 (6.5, NR)

CI = confidence interval; CR = complete response; DOR = duration of response; Id = idelalisib; IRC = independent review committee; NR = not reached; O = ofatumumab; PR = partial response
Analysis included only subjects who achieved a CR or PR.
Subjects with CR or PR who maintain the response for at least 8 weeks (with one with interval) are defined to have confirmed response for CR or PR. Otherwise, response status is categorized to SD.
a DOR (months) = (minimum [date of PD, date of death] – date of first documented CR or PR + 1) / 30.4375
Source: Section 15.1, Table 2.7.1

- **Best Percent Change in SPD**

Table 23: Best Percent Change in SPD by IRC Assessment - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)
Baseline		
N	174	87
Mean (StD)	6528.3 (6391.95)	8455.6 (7344.48)
Median	4823.0	6336.7
Q1, Q3	2532.8, 8166.1	3253.0, 11333.9
Min, Max	298.1, 44383.3	343.7. 35241.1
Best % Change		
N	164	81
Mean (StD)	-72.1 (13.63)	-11.2 (31.64)
Median	-74.6	-13.1
Q1, Q3	-82.5, -65.0	-29.3, 0.1
Min, Max	-94.5, -16.4	-73.6, 140.0

Id = idelalisib; IRC = independent review committee; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; SPD = sum of the products of greatest perpendicular diameters; StD = standard deviation
The tumor measurement from the first reader was used, unless the adjudicator picked the second reader.
Baseline was defined as the last measurement before randomization.
The best percent change from baseline was defined as the largest decrease in SPD postbaseline. For subjects who had SPD increases only, the smallest increase was considered the best change from baseline.
Source: Section 15.1, Table 2.8

Figure 7: Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment: Idelalisib + Ofatumumab Group - Study GS-US-312-0119 (ITT Analysis Set)

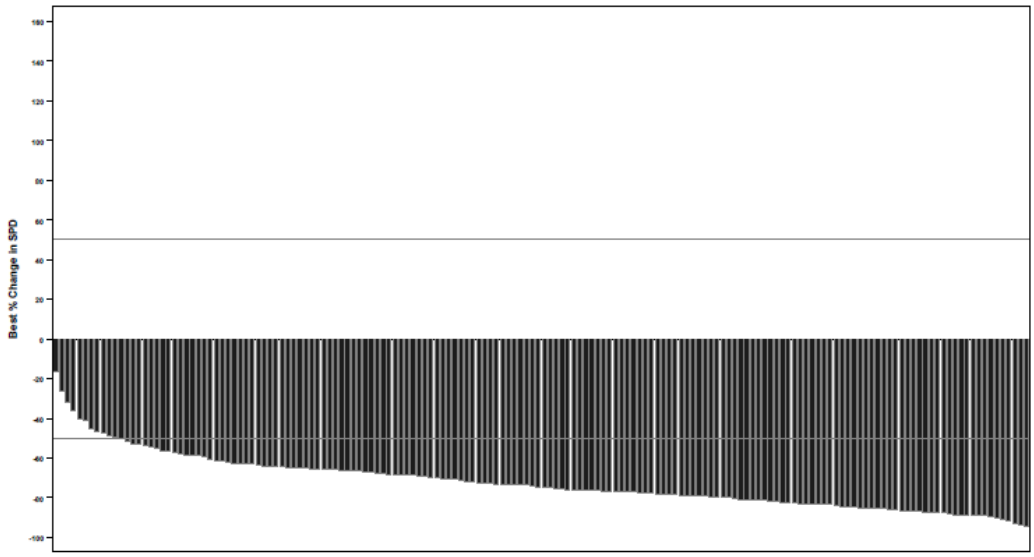
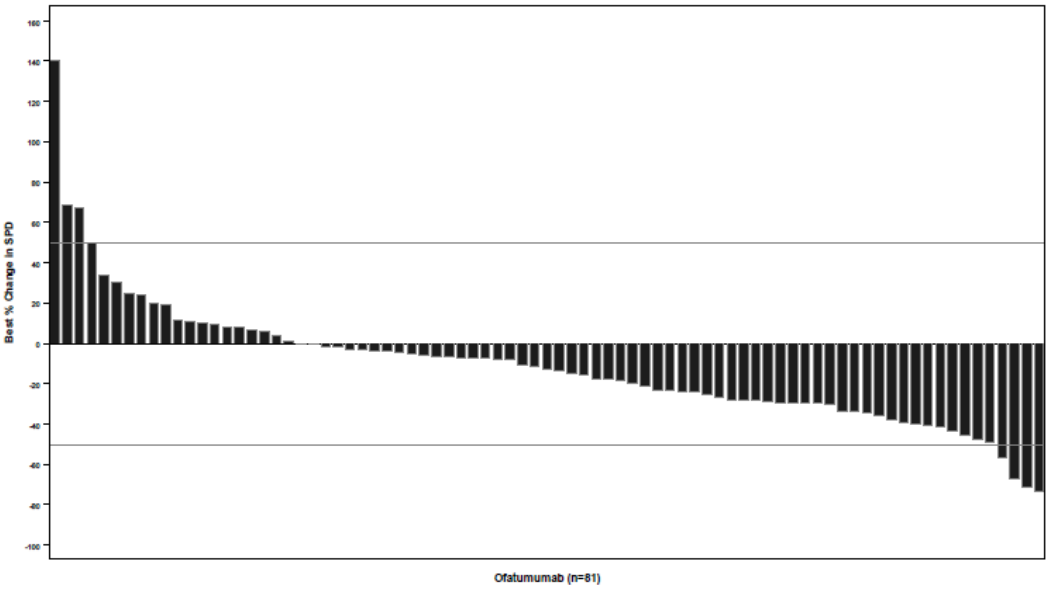


Figure 8: Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment: Ofatumumab Alone Group - Study GS-US-312-0119 (ITT Analysis Set)



- **Splenomegaly and Hepatomegaly Response Rates**

Table 24: Splenomegaly and Hepatomegaly Response Rates - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)
Splenomegaly Response Rate[a]	100/122 (82.0%)	24/56 (42.9%)
95% CI[b]	74, 88.3	29.7, 56.8
Hepatomegaly Response Rate[c]	56/86 (65.1%)	11/44 (25.0%)
95% CI[b]	54.1, 75.1	13.2, 40.3

CI = confidence interval; Id = idelalisib; O = ofatumumab

a Analysis included only subjects in the ITT Analysis Set 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 at least 1 evaluable postbaseline liver measurement.Hepatomegaly response rate was the percentage of 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.

Source: Section15.1, Tables 2.9.2 and 2.9.3

- **ALC, Platelet, Haemoglobin, and ANC Response Rates**

Table 25: ALC, Platelet, Haemoglobin, and ANC Response Rates - Study GS-US-312-0119 (ITT Analysis Set)

	Id + O (N = 174)	O (N = 87)
ALC Response Rate[a]	139/143 (97.2%)	60/68 (88.2%)
95% CI[b]	93, 99.2	78.1, 94.8
Platelet Response Rate[c]	88/93 (94.6%)	34/43 (79.1%)
95% CI[b]	87.9, 98.2	64, 90
Hemoglobin Response Rate[d]	65/73 (89.0%)	21/42 (50.0%)
95% CI[b]	79.5, 95.1	34.2, 65.8
ANC Response Rate[e]	31/32 (96.9%)	14/22 (63.6%)
95% CI[b]	83.8, 99.9	40.7, 82.8

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; CI = confidence interval; Id = idelalisib; O = ofatumumab

a Analysis included subjects who had lymphocytosis (ALC $\geq 4 \times 10^9$/L) at baseline. Responders were subjects with baseline lymphocytosis who achieved on-study ALC $< 4 \times 10^9$/L or $\geq$ 50% decrease in ALC from baseline.

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

c Analysis included subjects who had thrombocytopenia (platelet count $< 100 \times 10^9$/L) at baseline. Responders were subjects with baseline thrombocytopenia who achieved on-study platelet count of $\geq 100 \times 10^9$/L or $\geq$ 50% increase in platelet count from baseline.

d Analysis included subjects who had anemia (hemoglobin < 110 g/L [11 g/dL]) at baseline. Responders were subjects with baseline anemia who achieved on-study hemoglobin $\geq$ 110 g/L (11 g/dL) or $\geq$ 50% increase in hemoglobin from baseline.

e Analysis included subjects in the ITT Analysis Set who had neutropenia (ANC $< 1.5 \times 10^9$/L) at baseline. Responders were subjects with baseline neutropenia who achieved on-study ANC of $\geq 1.5 \times 10^9$/L or $\geq$ 50% increase in ANC from baseline.

Source: Section 15.1, Tables 2.9.4 through 2.9.7

- **Health-Related Quality of Life (HRQL) measures**

FACT-Leu Questionnaire Results

Mean (standard error of the mean, SEM) scores for the Additional Concerns, FACT Total Subscale, and the Trial Outcome Index were presented. In both treatment groups, postbaseline scores higher than baseline scores were observed; however, subjects in the idelalisib + ofatumumab group consistently showed greater symptom improvement than those in the ofatumumab alone group at each timepoint throughout the first 48 weeks of the study. Beyond Week 48, the number of subjects evaluated becomes too small for meaningful comparison.

Subjects treated with idelalisib + ofatumumab reached the MID for Additional Concerns (ie, 5-point improvement) at Week 4 (median change from baseline) and their improvement was generally sustained through Week 36, whereas subjects in the ofatumumab alone group reached the MID from Week 6 to Week 8 but had median values below the MID thereafter. In the mixed-effects model analysis of the changes from baseline, the main effect of treatment was statistically significant for the Total score, Trial Outcome Index score, and Additional Concerns subscale score (p = 0.0043, 0.0042, and 0.0016, respectively).

Karnofsky Performance Status

Table 26: Karnofsky Performance Status – Observed and Change from Baseline, ITT Analysis Set- Study GS-US-312-0119

		Id + O (N = 174)		O (N = 87)	
	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	n	173		87	
	Mean (StD)	84.2 (10.34)		82.9 (9.75)	
	95% CI	(82.6, 85.7)		(80.8, 85.0)	
	Median	80.0		80.0	
	Q1, Q3	80.0, 90.0		80.0, 90.0	
	Min. Max	60.0, 100.0		60.0, 100.0	
Best Change from Baseline[a]	n	173	173	86	86
	Mean (StD)	92.1 (8.78)	7.8 (9.57)	89.4 (9.62)	6.6 (9.02)
	95% CI	(90.8, 93.4)	(6.4, 9.2)	(87.4, 91.5)	(4.7, 8.6)
	Median	90.0	10.0	90.0	10.0
	Q1, Q3	90.0, 100.0	0.0, 10.0	90.0, 100.0	0.0, 10.0
	Min. Max	50.0, 100.0	-20.0, 40.0	60.0, 100.0	-20.0, 40.0

CI = confidence interval; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation

a Best change from baseline is defined as the highest value of change from baseline among all post-baseline visits.

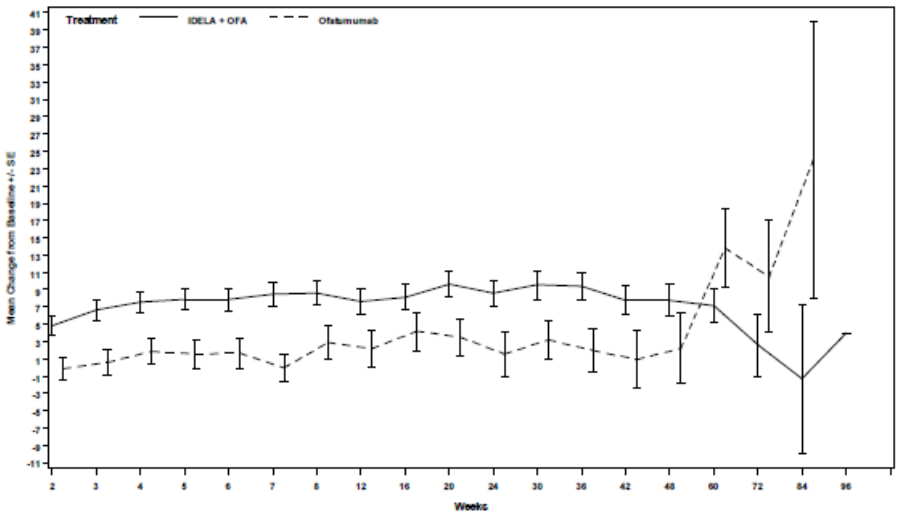
Source: Section 15.1, Table 2.11.2.1

Median improvement from baseline was similar in the 2 treatment groups (median best change from baseline of 10 points in both groups).

EQ-5D Questionnaire Results

As assessed by the EQ VAS, subjects on idelalisib + ofatumumab showed improvement over baseline than subjects on ofatumumab alone throughout the first 48 weeks of the study.

Figure 9: Mean (SEM) Change from Baseline in the EQ VAS - Study GS-US-312-0119 (ITT Analysis Set)



Ancillary analyses

Efficacy evaluation

A comparison of the efficacy data from studies GS-US-312-0116, which evaluated patients treated with idelalisib+rituximab vs rituximab and GS-US-312-0119, evaluating patients treated with idelalisib+ofatumumab vs ofatumumab. The following tables and figure represent the summary of the PFS and OS data, respectively.

Table 27: PFS by IRC Assessment - Studies GS-US-312-0116 and GS-US-312-0119 (ITT Analysis Set)

	GS-US-312-0116		GS-US-312-0119	
	Id + R (N=110)	Placebo + R (N=110)	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects with Events	25 (22.7)	70 (63.6)	76 (43.7)	54 (62.1)
Disease Progression	17 (15.5)	62 (56.4)	54 (31.0)	48 (55.2)
Death	8 (7.3)	8 (7.3)	22 (12.6)	6 (6.9)
Number (%) of Subjects Censored	85 (77.3)	40 (36.4)	98 (56.3)	33 (37.9)
Ongoing	--	--	75 (43.1)	4 (4.6)
Completed Study/Crossed over to Open-Label Idelalisib	69 (62.7)	33 (30.0)	--	--
Discontinued Study	16 (14.5)	7 (6.4)	21 (12.1)	29 (33.3)
Received Another Antitumor Treatment	0	0	0	0
Missed ≥ 2 Consecutive Tumor Measurements	0	0	2 (1.1)	0

	GS-US-312-0116		GS-US-312-0119	
	Id + R (N=110)	Placebo + R (N=110)	Id + O (N = 174)	O (N = 87)
KM Estimate of PFS (Months)[a]				
Q1 (95% CI)	10.7 (8.3, 13.9)	3.5 (1.8, 3.8)	9.0 (7.5, 10.8)	3.5 (1.8, 5.3)
Median (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)	16.3 (13.6, 17.8)	8.0 (5.7, 8.2)
Q3 (95% CI)	NR (19.4, NR)	8.3 (8.1, 10.9)	NR (17.8, NR)	9.2 (8.2, 16.4)
Adjusted Hazard Ratio (95% CI)[b]	0.15 (0.09, 0.24)		0.27 (0.19, 0.39)	
P-value[c]	< 0.0001		< 0.0001	

CI = confidence interval; Id = idelalisib; KM = Kaplan-Meier; NR = not reached; O = ofatumumab; PFS = progression-free survival; R = rituximab

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 (17p deletion/TP53 mutation and IGHV mutation).

c P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IGHV mutation).

Figure 10: Kaplan-Meier Curve of PFS by IRC Assessment – Study GS-US-312-0116 and GS-US-312-0119 (ITT Analysis Set)

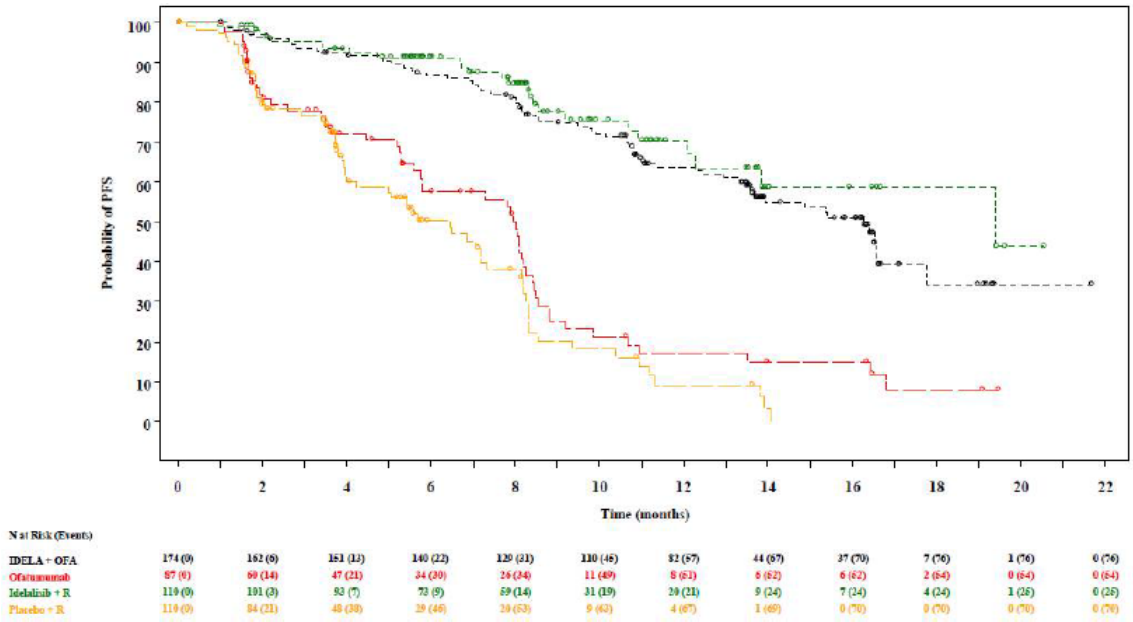


Table 28: Overall Survival - Studies GS-US-312-0116 and GS-US-312-0119 (ITT Analysis Set)

	GS-US-312-0116		GS-US-312-0119	
	Id + R (N=110)	Placebo + R (N=110)	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects Who Died	17 (15.5)	40 (36.4)	42 (24.1)	22 (25.3)

	GS-US-312-0116		GS-US-312-0119	
	Id + R (N=110)	Placebo + R (N=110)	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects Censored	93 (84.5)	70 (63.6)	132 (75.9)	65 (74.7)
Ongoing	60 (54.5)	38 (34.5)	84 (48.3)	6 (6.9)
Discontinued Study	33 (30.0)	32 (29.1)	48 (27.6)	59 (67.8)
KM Estimate of OS (Months)[a]				
Q1 (95% CI)	19 (16.6, NR)	9.2 (7.3, 12.6)	15.8 (11.4, 20.9)	13 (6.0, 19.4)
Median (95% CI)	NR (NR, NR)	20.8 (14.8, NR)	20.9 (20.9, NR)	19.4 (16.9, NR)
Q3 (95% CI)	NR (NR, NR)	NR (20.8, NR)	NR (20.9, NR)	NR (19.4, NR)
Adjusted Hazard Ratio (95% CI)[b]	0.34 (0.19, 0.60)		0.74 (0.44, 1.25)	
P-value From Stratified Log-Rank Test	0.0001		0.27	
Subgroup Factors (Unadjusted Hazard Ratio)[c]				
17p deletion and/or TP53 Mutation (Either)	0.31 (0.15, 0.65)		0.56 (0.27, 1.16)	
17p deletion and/or TP53 Mutation (Neither)	0.38 (0.16, 0.93)		0.94 (0.45, 2)	
Mutated IGHV	0.38 (0.07, 2.10)		1.26 (0.3, 5.24)	
Unmutated IGHV	0.35 (0.19, 0.63)		0.72 (0.41, 1.25)	
17p deletion	0.40 (0.17, 0.95)		0.62 (0.25, 1.54)	
No 17p deletion	0.31 (0.14, 0.67)		0.75 (0.39, 1.42)	

CI = confidence interval; Id = idelalisib; IGHV = immunoglobulin heavy chain variable region gene; KM = Kaplan-Meier; NR = not reached; O = ofatumumab; PFS = progression-free survival; R = rituximab

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

P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IGHV mutation).

Influence of Discontinuation Rates on Efficacy Endpoints

A summary of study duration for the ITT Analysis Set is shown in Table 20. Median study duration was over twice as long in the idelalisib + ofatumumab group (13.6 months) compared to the ofatumumab alone group (5.8 months). The discontinuation rate without a PFS event was 13.2% (23 subjects [including 2 subjects who missed ≥2 consecutive tumor measurements]) in the idelalisib + ofatumumab group and 33.3% (29 subjects) in the ofatumumab alone group.

A Kaplan-Meier analysis of time to discontinuation from study is shown in Figure 11.

Table 29: Duration of Study - Study GS-US-312-0119 (ITT Analysis Set)

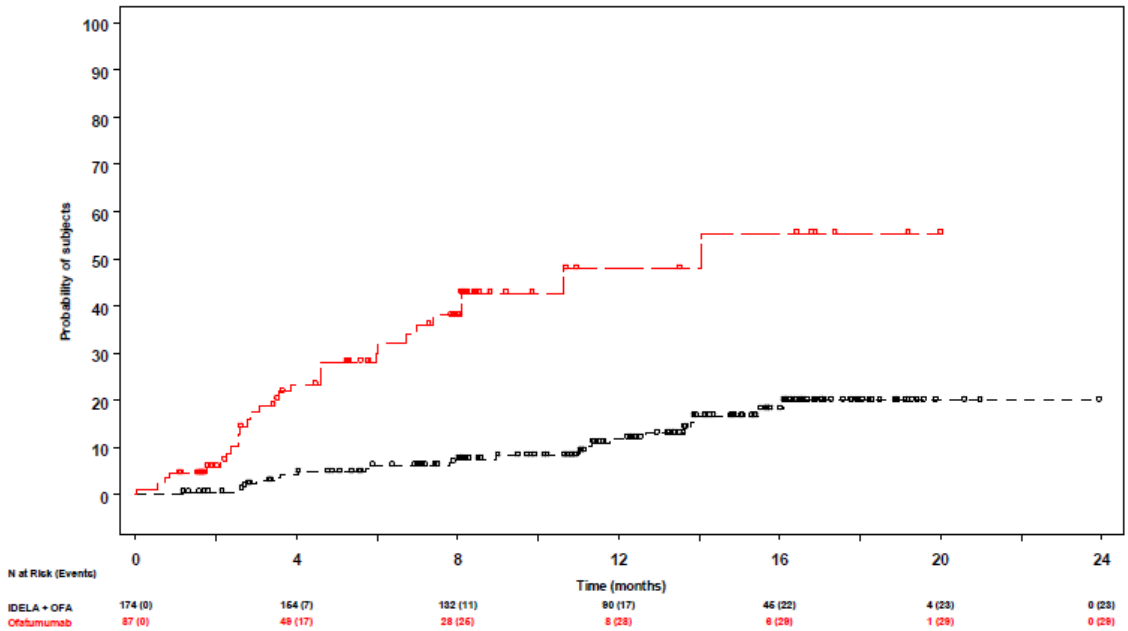
Study Duration (Months)[a]	Id + O (N = 174) n (%)	O (N = 87) n (%)
N	174	87
Mean (StD)	12.4 (5.17)	6.7 (4.81)
Median	13.6	5.8
Q1, Q3	9.2, 16.2	2.7, 9.7
Min, Max	1.1, 24.0	0.0, 20.0

Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation

a Duration of study (months) = (min (end of study date, data cutoff date) – date of randomization + 1) / 30.4375

Source: Section 15.1, Table 1.14

Figure 11: Kaplan-Meier Curve of Time to Discontinuation from Study - Study GS-US-312-0119 (ITT Analysis Set)



Summary of main study

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

Table 26: Summary of Efficacy for trial GS-US-312-0119

Title: A Phase 3, randomized, controlled study evaluating the efficacy and safety of Idelalisib (GS-1101) in combination with ofatumumab for previously treated Chronic Lymphocytic Leukemia		
Study identifier	GS-US-312-0119	
Design	Randomised (2:1), open-label	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks (both arms) not applicable not applicable
Hypothesis	Superiority	

Treatments groups	Experimental arm		Idelalisib (until CLL progression)+ ofatumumab (24 weeks) N=173
	Control arm		ofatumumab (24 weeks) N=86
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause
	Key Secondary endpoint	Overall response rate (ORR)	the proportion of subjects who achieved a CR or PR and maintained their response for at least 8 weeks (with 1 week window)
	Key Secondary endpoint	Lymph node response (LNR) rate	the proportion of subjects who achieved a $\geqslant$ 50% decrease from baseline in the SPD of index lesions per IRC assessments
	Key Secondary endpoint	Overall survival (OS)	the interval from randomization to death from any cause during the study
	Secondary endpoint	PFS in the Subgroup of Subjects with 17p Deletion and/or TP53 Mutation	the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause for 17p deleted and/or TP53 mutated subjects as collected in eCRF.
Data cut-off	**15-Jan-2015**		

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT)		
Descriptive statistics and estimate variability	Treatment group	Idelalisib + ofatumumab	ofatumumab
	Number of subject	174	87
	PFS (months)	16.3	8.0
	95% CI	13.6, 17.8	5.7, 8.2
	ORR	75.3	18.4
	95% CI	68.2, 81.5	10.9, 28.1
	LNR rate 95% CI	93.3 88.3, 96.6	4.9 1.4, 12.2
	OS (months) 95% CI	20.9 (20.9, NR)	19.4 16.9, NR
	PFS in the Subgroup of Subjects with 17p Deletion and/or TP53 Mutation	(N=70) 13.7	(N=33) 5.8
	95% CI	11, 17.8	4.5, 8.4
Effect estimate per comparison	PFS	Comparison groups	Idelalisib + ofatumumab vs ofatumumab

		Odds ratio	0.27
		95% CI	0.19,0.39
		P-value	<0.0001
	ORR	Comparison groups	Idelalisib + ofatumumab vs ofatumumab
		Odds Ratio	15.94
		95% CI	7.8, 32,58
		P-value	<0.0001
	LNR rate	Comparison groups	Idelalisib + ofatumumab vs ofatumumab
		Odds Ratio	486.96
		95% CI	97.91,2421.85
		P-value	<0.0001
	OS	Comparison groups	Idelalisib + ofatumumab vs ofatumumab
		HR	0.75
		95% CI	0.48, 1.18
		P-value	0.27
	PFS in the Subgroup of Subjects with 17p Deletion and/or TP53 Mutation	Comparison groups	Idelalisib + ofatumumab vs ofatumumab
		HR	0.29
		95% CI	0.18, 0.46
		P-value	<0.0001
Notes	Stratification factors: 1)17p deletion and/or TP53 mutation in CLL cells: either versus neither (or indeterminate); 2) IGHV mutation: unmutated (or IGHV3-21) versus mutated (or indeterminate); 3)Disease status: refractory (CLL progression < 6 months from completion of prior therapy) versus relapsed (CLL progression ≥6 months from completion of prior therapy)		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

GS-US-312-0119, a Phase 3 randomised open-label study evaluating the efficacy and safety of idelalisib in combination with ofatumumab in previously treated CLL patients was initiated on 4 December 2012, and ran almost parallel to the other Phase 3 study GS-US-312-0116 which was initiated on 01 May 2012. Both studies were conducted in patients with previously treated CLL and randomised between treatment with idelalisib in combination with either rituximab (GS-US-312-0116) or ofatumumab (GS-US-312-0119) and their respective monotherapy controls.

A total of 261 subjects in study GS-US-312-0119 were randomised in a 2:1 ratio (174 to the idelalisib + ofatumumab group, 87 to the ofatumumab alone group). There were 261 subjects included in the ITT Analysis Set, and 259 subjects included in the Safety Analysis Set.

A total of 173 subjects received treatment with idelalisib + ofatumumab. At the time of the interim analysis (the final analysis for PFS), 43.1% (75 subjects) of the idelalisib + ofatumumab group were continuing idelalisib treatment, 43.7% (76 subjects) were not continuing treatment due to meeting the primary endpoint, and 12.1% (21 subjects) had discontinued treatment for other reasons.

Investigators cited AEs as the reason for discontinuation from treatment in 29.3% (51 subjects) in the idelalisib + ofatumumab group.

Of subjects reported by the investigator to have discontinued the study without an event, 20/34 in the idelalisib + ofatumumab arm and 7/34 in the ofatumumab arm were (later) assessed to have had an event (most likely PD) by the IRC.

Of the 87 patients allocated to the ofatumumab arm, 6 (6.9%) were still ongoing, 47 (54%) were not continuing treatment due to meeting the primary endpoint, and 34 (39.1%) had discontinued treatment for other reasons.

In both treatment groups, the primary reasons for discontinuation were physician decision (10.0% [19 subjects] of the idelalisib + ofatumumab group and 18.4% [16 subjects] of the ofatumumab alone group) followed by withdrawal by subject (6.9% [12 subjects] of the idelalisib + ofatumumab group and 16.1% [14 subjects] of the ofatumumab alone group). Median study duration was over twice as long in the idelalisib + ofatumumab group (13.6 months) compared to the ofatumumab alone group (5.8 months).

Overall, demographics and baseline characteristics (age, sex, race, BMI) were generally comparable between the 2 treatment groups. Most subjects (64.0%) were ≥ 65 years of age, with a median (Q1, Q3) age of 68 (61, 74) years, and an age range of 36 to 85 years. Most subjects (71.3%) were male and most were white (84.3%). Almost all subjects (226 subjects; 86.6%) had a reduced Karnofsky Performance Status. Median time since diagnosis was 7.7 (4.8, 10.8) years. At study screening, most subjects had advanced disease, with 63.6% Rai Stage III or IV and 58.2% Binet Stage C. Disease characteristics were balanced between treatment groups. In the total population, 55.2% of subjects had platelet counts < 100 × 10^9/L at screening, 47% had hemoglobin < 11 g/dL, and 22.4% had ANC < 1.5 × 10^9/L; the median (Q1, Q3) CIRS score at screening was 4.0 (2.0, 7.0). The strata of 17p deletion and/or TP53 mutation and IGHV mutation status were well-balanced between treatment groups. Median number of prior treatments was 3.0 in each arm with a range of 1 to 11. The most frequent prior treatments were bendamustine + rituximab (29%), fludarabine + cyclophosphamide + rituximab (22%) and fludarabine + rituximab (5.4%), and treatment groups were balanced with respect to the incidence and type of prior CLL regimens.

Due to a stratification error (see section on conduct of the study – protocol deviations), a lower percentage of refractory subjects (47.1% v. 54.0) was enrolled of the idelalisib + ofatumumab group as compared with the ofatumumab alone group. The primary efficacy analyses presented in this report were stratified according to this factor.

The dose of ofatumumab (1000 mg/infusion) used in combination with idelalisib (Group A) in Study GS-US-312-0119 was supported by previously reported nonclinical target-saturation data and clinical data for ofatumumab when administered to subjects with relapsed/refractory CLL in combination with bendamustine, lenalidomide and other agents. The dose of ofatumumab as a single agent (2000 mg/infusion) (Group B) is consistent with the approved dosing regimen for patients with refractory CLL.

Thus, the doses of ofatumumab were different in the 2 treatment arms. This is unlike the GS-US-312-0116 study, where subjects were randomised between idelalisib + rituximab or rituximab only. In that study, both treatment arms were administered 8 infusions of rituximab (every 2 weeks for 4 infusions and every 4 weeks for a further 4 infusions).

Efficacy data and additional analyses

The analysis of the primary endpoint PFS was based on the ITT Analysis Set and stratified by 17p deletion and/or TP53 mutation, IGHV mutation, and disease status. With an overall event rate of ~50%, a total of 43.7% (76 subjects) of the idelalisib + ofatumumab group and 62.1% (54 subjects) of the ofatumumab alone group experienced a PFS event, with an adjusted HR (95% CI) of 0.27 (0.19, 0.39) and 2-sided p-value of < 0.0001 based on a stratified log-rank test. The median PFS (95% CI) was 16.3 (13.6, 17.8) months for subjects in the idelalisib + ofatumumab group and 8.0 (5.7, 8.2) months for subjects in the ofatumumab alone group. Although the data are not yet mature, it seems unlikely that the difference in PFS between the arms will undergo any dramatic change. There are few remaining subjects as a high number of patients discontinued without event. Therefore, a substantial change to the median PFS in the control arm seems unlikely.

The PFS advantage for the idelalisib + ofatumumab arm seems not to be dependent on the presence or absence of del17p/TP53-mutation. Based on the IRC assessment (ITT Analysis Set), the ORR (classified as CR or PR) (95% CI) was 75.3% (68.2%, 81.5%) for the idelalisib + ofatumumab group and 18.4% (10.9%, 28.1%) for the ofatumumab alone group. The odds ratio (95% CI) for the ORR was 15.94 (7.8, 32.58), which favored idelalisib + ofatumumab compared with ofatumumab alone (p < 0.0001). Only 1 patient achieved a CR in the study.

The primary OS analysis was performed using the ITT Analysis Set. As of the data cutoff date, a total of 64 subjects had died (42 subjects [24.1%] in the idelalisib + ofatumumab group and 22 subjects [25.3%] in the ofatumumab alone group). The adjusted HR (95% CI) for OS was 0.74 (0.44, 1.24); p = 0.27. Therefore, no significant differences were found between the 2 treatment arms of the idelalisib-ofatumumab study. This is in contrast with the GS-US-312-0116 study where the adjusted HR between the arms was 0.34 with a p-value of 0.0001 using a stratified log-rank test. Subgroup analyses showed a great consistency between all subgroups of high risk prognostic markers (17p deletion and/or TP53 mutation (either/neither), mutated IGHV, unmutated IGHV, 17p deletion/no deletion). The CHMP raised this as a concern, and whether informative censoring or other factors may have contributed to the negative results observed with OS in study GS-US-312-0119.

The MAH provided several additional analyses aiming to explore whether informative censoring or other factors may have contributed to the negative results observed with OS in study GS-US-312-0119. These analyses showed that the disproportionate number of discontinued patients in the two treatment arms (39.1% in the ofatumumab alone group vs 19.5% in the idelalisib+ofatumumab group) could have undermined the integrity of this analysis and that the lack of statistically significant result in OS might be, at least partly, explained by a larger proportion of subjects in the control arm discontinuing treatment early and receiving rescue therapy (with eg BCR inhibitors) after a progressive disease event or after discontinuing without an event. It is likely that many subjects in the control arm who discontinued the open-labeled study GS-US-312-0119, which started approximately half a year after placebo-controlled study GS-US-312-0116, had subsequent access to idelalisib or other novel CLL therapies, confounding the OS analysis in this study. In addition, a direct comparison between the two studies is complicated by the different lengths of follow-up. This might have been partly overcome had the MAH submitted data from the extension study GS-US-312-0117 (a follow-up to GS-US-312-0116). Nonetheless, the CHMP was reassured that the robust PFS data from study GS-US-312-0119, which is similar and comparable to that observed in the controlled and blinded study GS-US-312-0116, provided sufficient evidence of a clinically relevant benefit in CLL patients.

Results for the HRQoL measures (mean scores for the Additional Concerns, FACT Total Subscale, and the Trial Outcome Index) showed that the idelalisib + ofatumumab group consistently showed greater symptom improvement than those in the ofatumumab alone group at each timepoint throughout the first 48 weeks of the study. However, there is a risk for bias in HRQoL assessments in an open-label

study. This would concern especially the results from FACT-Leu and the EQ-5D and EQ-VAS. Therefore, no clear conclusion can be drawn on the HRQoL data.

2.4.3. Conclusions on the clinical efficacy

Clinical efficacy of the combination of idelalisib with ofatumumab has been shown in terms of an advantange of 8 months in PFS in study GS-US-312-0119 which was statistically significant and clinically important and seems robust, although the overall event rate is still not mature at around 50%. The higher efficacy of idelalisib + ofatumumab appears consistent in all subgroups including notably patients with high-risk prognostic features such as del 17p/TP53-mutations and those with unmutated IgHV-chains.

No difference in OS between the 2 treatment arms was seen in the study. This is in contrast with the almost parallel study GS-US-312-0116 where idelalisib + rituximab was compared with placebo + rituximab, and where the KM estimate of OS indicated a clearly significant advantage of the idelalisib + rituximab arm.

2.5. Clinical safety

Introduction

Clinical safety of idelalisib was evaluated in the pivotal Study GS-US-312-0119 in subjects with previously treated CLL. All safety analyses were performed using the safety population, defined as all subjects who received at least 1 dose of study drug, in accordance with the study-specific statistical analysis plan (SAP).

Safety data from the pivotal study are supported by data from the randomised, placebo-controlled Study GS-US-312-0116 and its extension, Study GS-US-312-0117; monotherapy data from Studies 101-02, 101-08 Cohort 2, 101-09, 101-10, and 101-11; and combination therapy data from Studies 101-07, 101-08 Cohort 1, and extension Study 101-99.

Patient exposure

Of the 261 subjects randomised in the study, 259 received at least 1 dose of idelalisib or ofatumumab and were evaluable for safety. All 261 subjects correctly received the treatment to which they were assigned during randomization.

The median (Q1, Q3) duration of exposure to idelalisib in the idelalisib + ofatumumab group was 12.3 (6.8, 16.1) months, with a range of 0.2 to 23.9 months (Table 30). The median (Q1, Q3) duration of exposure to ofatumumab was 5.3 (5.3, 5.4) months in the idelalisib + ofatumumab group and was 4.2 (1.6, 5.3) months in the ofatumumab alone group.

Table 30: Idelalisib Exposure (Safety Analysis Set) - Study GS-US-312-0119

	Id + O (N = 173)
Duration of Exposure to Idelalisib (Months)[a]	
N	173
Mean (StD)	11.5 (5.73)
Median	12.3
Q1, Q3	6.8, 16.1
Min, Max	0.2, 23.9
Cumulative Exposure to Idelalisib, n (%)	
≥ 1 Day	173 (100.0)
≥ 2 months	161 (93.1)
≥ 4 months	144 (83.2)
≥ 6 months	134 (77.5)
≥ 12 months	90 (52.0)
≥ 18 months	19 (11.0)
Adherence (%) Category[b], n (%)	
≥ 75%	172 (99.4)
< 75%	1 (0.6)
Subjects with No Dose Modification, n (%)	80 (46.2)
Subjects with Dose Modification, n (%)	93 (53.8)

Table 31: Ofatumumab Exposure (Safety Analysis Set) - Study GS-US-312-0119

	Id + O (N = 173)	O (N = 86)	Total (N = 259)
Duration of Exposure to Ofatumumab (Months)[a]			
N	173	86	259
Mean (StD)	4.8 (1.44)	3.6 (1.87)	4.4 (1.69)
Median	5.3	4.2	5.3
Q1, Q3	5.3, 5.4	1.6, 5.3	3.5, 5.4
Min, Max	0.0, 7.0	0.3, 6.7	0.0, 7.0
Cumulative Exposure to Ofatumumab			
≥ 1 Day	173 (100.0)	86 (100.0)	259 (100.0)
≥ 2 months	154 (89.0)	57 (66.3)	211 (81.5)
≥ 4 months	144 (83.2)	44 (51.2)	188 (72.6)
≥ 5 months	139 (80.3)	39 (45.3)	178 (68.7)
≥ 6 months	4 (2.3)	1 (1.2)	5 (1.9)
Adherence Category			
≥ 75%	152 (87.9)	55 (64.0)	207 (79.9)
< 75%	21 (12.1)	31 (36.0)	52 (20.1)
Number of Ofatumumab Doses			
N	173	86	259
Mean (StD)	10.9 (2.34)	9.6 (2.86)	10.5 (2.60)
Median	12.0	10.5	12.0
Q1, Q3	11.0, 12.0	8.0, 12.0	10.0, 12.0
Min, Max	1.0, 12.0	2.0, 12.0	1.0, 12.0

Adverse events

Adverse Events (AEs) were defined as events that met 1 of the following criteria:

- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study medication from each specified study phase;
- Continuing AEs diagnosed prior to the start of treatment and worsening in severity grade after the start of treatment, non-serious AEs at baseline becoming serious after the start of treatment, or AEs resulting in treatment discontinuation after the start of treatment.

Treatment-related AEs (adverse drug reactions) are defined as events assessed by the investigator as having a causal relationship to idelalisib of related, definite, probable, or possible.

The only event reported for ≥ 20% of subjects was diarrhea (25.4%). A summary of AEs assessed by the investigator as related to treatment with idelalisib reported for ≥ 10% of subjects treated with idelalisib plus an anti-CD20 agent in Studies GS-US-312-0119 and GS-US-312-0116 is presented in Table 32.

Table 32: Adverse Events reported for >10% of subjects treated with idelalisib plus rituximab or ofatumumab in studies GS-US-312-0119 and GS-US-312-0116 (safety analysis set)

Preferred Term[a]	Idelalisib + Anti-CD20[b] (N = 283) n (%)	Anti-CD20 Only[c] (N = 194) n (%)
Subjects with any AE[d,e]	280 (98.9)	191 (98.5)
Diarrhoea	115 (40.6)	39 (20.1)
Fatigue	89 (31.4)	59 (30.4)
Pyrexia	100 (35.3)	40 (20.6)
Cough	79 (27.9)	52 (26.8)
Nausea	83 (29.3)	48 (24.7)
Neutropenia	89 (31.4)	35 (18.0)
Infusion Related Reaction	51 (18.0)	56 (28.9)
Chills	51 (18.0)	30 (15.5)
Constipation	52 (18.4)	29 (14.9)
Dyspnoea	46 (16.3)	32 (16.5)
Pneumonia	46 (16.3)	26 (13.4)
Anaemia	49 (17.3)	21 (10.8)
Decreased Appetite	48 (17.0)	19 (9.8)
Upper Respiratory Tract Infection	41 (14.5)	24 (12.4)
Headache	44 (15.5)	19 (9.8)
Vomiting	42 (14.8)	21 (10.8)
Rash	49 (17.3)	12 (6.2)
Oedema Peripheral	41 (14.5)	19 (9.8)
Insomnia	37 (13.1)	20 (10.3)
Abdominal Pain	37 (13.1)	17 (8.8)
Asthenia	32 (11.3)	20 (10.3)
Back Pain	29 (10.2)	15 (7.7)
Hypokalaemia	33 (11.7)	10 (5.2)
Urinary Tract Infection	33 (11.7)	10 (5.2)
Weight Decreased	29 (10.2)	14 (7.2)
Thrombocytopenia	30 (10.6)	11 (5.7)

a Subjects who experienced multiple events with the same PT were counted once per PT.
b Subjects who received Id+O in Study GS-US-312-0119 or Id+R in Study GS-US-312-0116.
c Subjects who received ofatumumab only in Study GS-US-312-0119 or placebo plus rituximab in Study GS-US-312-0116.
d For subjects in Study GS-US-312-0119, events had onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study treatment, or AEs resulting in treatment discontinuation after the start of treatment.
e For subjects in Study GS-US-312-0116, events had onset dates on or after the start of treatment and up to the day before the first dose of open-label idelalisib.

Table 33: Overall summary of adverse events (Safety Analysis Set) - Study GS-US-312-0119

Adverse Event Category, n (%)	Id + O (N = 173)	O (N = 86)
Any AE	172 (99.4)	85 (98.8)
≥ Grade 3 AE	152 (87.9)	48 (55.8)
Idelalisib-Related AE	155 (89.6)	NA
≥ Grade 3 Idelalisib-Related AE	116 (67.1)	NA
Ofatumumab-Related AE	136 (78.6)	67 (77.9)
≥ Grade 3 Ofatumumab-Related AE	82 (47.4)	29 (33.7)
AE Related to both Idelalisib and Ofatumumab	102 (59.0)	NA
Any SAE	121 (69.9)	36 (41.9)
Idelalisib-Related SAE	73 (42.2)	NA
Ofatumumab-Related AE	39 (22.5)	17 (19.8)
AE That Led to Idelalisib Dose Reduction	35 (20.2)	NA
AE That Led to Idelalisib Dose Interruption	93 (53.8)	NA
AE That Led to Idelalisib Dose Interruption/Reduction	97 (56.1)	NA
AE That Led to Idelalisib Discontinuation	53 (30.6)	NA
AE That Led to Ofatumumab Delayed	79 (45.7)	20 (23.3)
AE That Led to Ofatumumab Discontinuation	16 (9.2)	20 (23.3)
Death due to AE	18 (10.4)	6 (7.0)

AE = adverse event; Id = idelalisib; NA = not applicable; O = ofatumumab; SAE = serious adverse event
Relationship to idelalisib is determined by investigator; AEs with missing relationships are considered to be related.
Source: Section 15.1, Table 3.1.1

Table 34: AEs reported by the investigator as related to idelalisib for ≥5% of subjects (Safety Analysis Set) – Study GS-US-312-0119

System Organ Class Preferred Term	Id + O (N = 173)
Number of Subjects with any AE Reported by the Investigator as Related to Idelalisib	155 (89.6)
Gastrointestinal disorders	92 (53.2)
Diarrhoea	57 (32.9)
Nausea	25 (14.5)
Constipation	14 (8.1)
Abdominal pain	13 (7.5)
Colitis	12 (6.9)
General disorders and administration site conditions	54 (31.2)
Fatigue	30 (17.3)
Pyrexia	18 (10.4)
Blood and lymphatic system disorders	53 (30.6)
Neutropenia	31 (17.9)
Febrile neutropenia	12 (6.9)
Thrombocytopenia	10 (5.8)
Anaemia	9 (5.2)
Infections and infestations	50 (28.9)
Pneumonia	12 (6.9)
Skin and subcutaneous tissue disorders	43 (24.9)
Rash	15 (8.7)
Rash maculo-papular	9 (5.2)
Investigations	42 (24.3)
Alanine aminotransferase increased	16 (9.2)
Aspartate aminotransferase increased	11 (6.4)
Neutrophil count decreased	10 (5.8)
Nervous system disorders	38 (22.0)
Headache	13 (7.5)
Dysgeusia	9 (5.2)
Metabolism and nutrition disorders	32 (18.5)
Decreased appetite	12 (6.9)

Respiratory, thoracic and mediastinal disorders	27 (15.6)
Cough	10 (5.8)
Pneumonitis	10 (5.8)[a]

Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT (or SOC) are counted once per PT (or SOC).

a Includes 1 event (in Subject [redacted]) with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease.

Table 35: Treatment-related AEs reported for ≥10% of subjects treated with idelalisib plus rituximab or ofatumumab in studies GS-US-312-0116 and GS-US-312-0116 (Safety Analysis Set)

Preferred Term[a]	Idelalisib + Anti-CD20[b] (N = 283) n (%)
Subjects with any Idelalisib-Related AE[c,d]	215 (76.0)
Diarrhoea	72 (25.4)
Fatigue	43 (15.2)
Neutropenia	42 (14.8)
Nausea	34 (12.0)

a Subjects who experienced multiple events with the same PT were counted once per PT.
b Subjects who received Id+O in Study GS-US-312-0119 or Id+R in Study GS-US-312-0116.
c For subjects in Study GS-US-312-0119, events had onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study treatment, or AEs resulting in treatment discontinuation after the start of treatment.
d For subjects in Study GS-US-312-0116, events had onset dates on or after the start of treatment and up to the day before the first dose of open-label idelalisib.

Frequent Adverse Events

Adverse events reported for ≥10% of subjects in either treatment group are summarized by SOC and PT by decreasing frequency for the Safety Analysis Set in Table 33.

The most commonly reported AEs by treatment group were as follows:

- idelalisib + ofatumumab: diarrhoea (48.0%, 83 subjects), neutropenia (35.3%, 61 subjects), and pyrexia (32.4%, 56 subjects)
- ofatumumab: fatigue (27.9%, 24 subjects), nausea and infusion related reaction (each 26.7%, 23 subjects), and diarrhoea and pyrexia (each 23.3%, 20 subjects)

Table 36: Adverse Events Reported for ≥10% of Subjects in Either Treatment Group by Decreasing SOC and PT (Safety Analysis Set- Study GS-US-312-0119)

Adverse Events by System Organ Class and Preferred Term	Id + O (N = 173) n (%)	O (N = 86) n (%)
Infections and Infestations	132 (76.3)	51 (59.3)
Pneumonia	30 (17.3)	11 (12.8)
Upper respiratory tract infection	31 (17.9)	9 (10.5)
Urinary tract infection	23 (13.3)	6 (7.0)
Sinusitis	19 (11.0)	2 (2.3)
Bronchitis	19 (11.0)	0
Gastrointestinal Disorders	124 (71.7)	51 (59.3)
Diarrhoea	83 (48.0)	20 (23.3)
Nausea	52 (30.1)	23 (26.7)
Constipation	36 (20.8)	13 (15.1)
Vomiting	25 (14.5)	12 (14.0)
Abdominal pain	26 (15.0)	6 (7.0)
General Disorders and Administration Site Conditions	122 (70.5)	56 (65.1)
Fatigue	55 (31.8)	24 (27.9)
Pyrexia	56 (32.4)	20 (23.3)
Oedema peripheral	29 (16.8)	9 (10.5)
Chills	24 (13.9)	13 (15.1)
Asthenia	23 (13.3)	10 (11.6)
Blood and Lymphatic System Disorders	96 (55.5)	28 (32.6)
Neutropenia	61 (35.3)	14 (16.3)
Anaemia	34 (19.7)	9 (10.5)
Thrombocytopenia	22 (12.7)	6 (7.0)
Febrile neutropenia	22 (12.7)	3 (3.5)
Respiratory, Thoracic and Mediastinal Disorders	95 (54.9)	38 (44.2)
Cough	52 (30.1)	18 (20.9)
Dyspnoea	29 (16.8)	10 (11.6)
Skin and Subcutaneous Tissue Disorders	89 (51.4)	30 (34.9)
Rash	34 (19.7)	7 (8.1)
Pruritus	19 (11.0)	6 (7.0)
Night sweats	7 (4.0)	10 (11.6)

Adverse Events by System Organ Class and Preferred Term	Id + O (N = 173) n (%)	O (N = 86) n (%)
Metabolism and Nutrition Disorders	80 (46.2)	20 (23.3)
Decreased appetite	30 (17.3)	7 (8.1)
Hypokalaemia	25 (14.5)	4 (4.7)
Nervous System Disorders	77 (44.5)	30 (34.9)
Headache	33 (19.1)	9 (10.5)
Musculoskeletal and Connective Tissue Disorders	73 (42.2)	32 (37.2)
Back pain	23 (13.3)	11 (12.8)
Investigations	76 (43.9)	18 (20.9)
Weight decreased	18 (10.4)	5 (5.8)
Injury, Poisoning and Procedural Complications	53 (30.6)	32 (37.2)
Infusion related reaction	29 (16.8)	23 (26.7)
Psychiatric Disorders	50 (28.9)	19 (22.1)
Insomnia	27 (15.6)	13 (15.1)

Id = idelalisib; O = ofatumumab
AE was classified by PT using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT (or SOC) were counted once per PT (or SOC).

Table 37: Adverse Events by Time Interval (Safety Analysis Set) - Study GS-US-312-0119

	0 to 12 Weeks		12 to 24 Weeks		24 to 36 weeks		36 to 48 Weeks[a]	> 48 Weeks[a]
Adverse Event, n (%)	Id + O (N = 173)	O (N = 86)	Id + O (N = 164)	O (N = 58)	Id + O (N = 144)	O (N = 40)	Id + O (N = 128)	Id + O (N = 111)
Diarrhoea	39 (22.5)	14 (16.3)	32 (19.5)	8 (13.8)	20 (13.9)	1 (2.5)	20 (15.6)	28 (25.2)
Fatigue	40 (23.1)	17 (19.8)	12 (7.3)	8 (13.8)	6 (4.2)	1 (2.5)	7 (5.5)	5 (4.5)
Pyrexia	33 (19.1)	16 (18.6)	18 (11.0)	2 (3.4)	14 (9.7)	2 (5.0)	12 (9.4)	7 (6.3)
Nausea	29 (16.8)	23 (26.7)	11 (6.7)	1 (1.7)	6 (4.2)	0	9 (7.0)	6 (5.4)
Neutropenia	38 (22.0)	13 (15.1)	26 (15.9)	4 (6.9)	17 (11.8)	0	14 (10.9)	9 (8.1)
Cough	28 (16.2)	16 (18.6)	15 (9.1)	4 (6.9)	12 (8.3)	0	6 (4.7)	8 (7.2)
Infusion related reaction	25 (14.5)	23 (26.7)	4 (2.4)	1 (1.7)	0	0	2 (1.6)	2 (1.8)
Constipation	28 (16.2)	10 (11.6)	5 (3.0)	3 (5.2)	5 (3.5)	0	1 (0.8)	7 (6.3)
Anaemia	22 (12.7)	9 (10.5)	6 (3.7)	0	5 (3.5)	0	5 (3.9)	7 (6.3)
Headache	22 (12.7)	7 (8.1)	4 (2.4)	1 (1.7)	5 (3.5)	1 (2.5)	7 (5.5)	5 (4.5)
Pneumonia	11 (6.4)	7 (8.1)	3 (1.8)	4 (6.9)	6 (4.2)	0	4 (3.1)	8 (7.2)
Rash	23 (13.3)	5 (5.8)	8 (4.9)	3 (5.2)	5 (3.5)	0	1 (0.8)	4 (3.6)
Insomnia	18 (10.4)	12 (14.0)	5 (3.0)	1 (1.7)	3 (2.1)	0	4 (3.1)	1 (0.9)
Upper respiratory tract infection	14 (8.1)	7 (8.1)	7 (4.3)	1 (1.7)	8 (5.6)	1 (2.5)	2 (1.6)	2 (1.8)
Dyspnoea	13 (7.5)	9 (10.5)	13 (7.9)	4 (6.9)	1 (0.7)	0	7 (5.5)	5 (4.5)
Oedema peripheral	12 (6.9)	8 (9.3)	5 (3.0)	2 (3.4)	4 (2.8)	0	3 (2.3)	9 (8.1)
Chills	13 (7.5)	10 (11.6)	5 (3.0)	5 (8.6)	3 (2.1)	0	2 (1.6)	3 (2.7)
Decreased appetite	13 (7.5)	6 (7.0)	6 (3.7)	1 (1.7)	3 (2.1)	0	5 (3.9)	5 (4.5)
Vomiting	10 (5.8)	11 (12.8)	8 (4.9)	2 (3.4)	6 (4.2)	0	4 (3.1)	3 (2.7)
Back pain	16 (9.2)	6 (7.0)	2 (1.2)	4 (6.9)	7 (4.9)	1 (2.5)	1 (0.8)	2 (1.8)
Asthenia	16 (9.2)	9 (10.5)	3 (1.8)	1 (1.7)	1 (0.7)	0	4 (3.1)	2 (1.8)
Abdominal pain	10 (5.8)	6 (7.0)	9 (5.5)	1 (1.7)	3 (2.1)	0	2 (1.6)	6 (5.4)
Hypokalemia	9 (5.2)	4 (4.7)	5 (3.0)	0	9 (6.3)	0	3 (2.3)	8 (7.2)
Urinary tract infection	5 (2.9)	4 (4.7)	7 (4.3)	2 (3.4)	4 (2.8)	0	4 (3.1)	8 (7.2)
Thrombocytopenia	11 (6.4)	6 (7.0)	2 (1.2)	0	4 (2.8)	0	5 (3.9)	5 (4.5)
Febrile neutropenia	9 (5.2)	3 (3.5)	3 (1.8)	0	7 (4.9)	0	3 (2.3)	6 (5.4)
Pruritus	15 (8.7)	6 (7.0)	3 (1.8)	0	2 (1.4)	0	0	1 (0.9)
Weight decreased	9 (5.2)	4 (4.7)	2 (1.2)	2 (3.4)	4 (2.8)	1 (2.5)	3 (2.3)	2 (1.8)
Sinusitis	7 (4.0)	2 (2.3)	3 (1.8)	0	4 (2.8)	0	4 (3.1)	5 (4.5)
Bronchitis	7 (4.0)	0	7 (4.3)	0	2 (1.4)	0	2 (1.6)	4 (3.6)
Night sweats	2 (1.2)	7 (8.1)	3 (1.8)	3 (5.2)	0	0	0	3 (2.7)

Id = idelalisib; O = ofatumumab

a Treatment-Emergent AEs were those within 30 days of treatment. Since O treatment ended at Week 24, no TEAEs were reported for the O group in these time windows.

AE was classified by PT using MedDRA version 17.1.

Subjects who experienced multiple events within the same PT were counted once per PT in the highest severity grade, obtained per CTCAE version 4.03.

Table 38: ≥Grade 3 AEs Reported for > 2% of Subjects in Either Treatment Group by Decreasing SOC and PT (Safety Analysis Set) - Study GS-US-312-0119

System Organ Class Preferred Term	Id + O (N = 173)	O (N = 86)
Subjects with ≥ Grade 3 AE	152 (87.9%)	48 (55.8%)
Blood and lymphatic system disorders	87 (50.3%)	22 (25.6%)
Neutropenia	59 (34.1%)	13 (15.1%)
Anaemia	20 (11.6%)	5 (5.8%)
Febrile neutropenia	20 (11.6%)	3 (3.5%)
Thrombocytopenia	16 (9.2%)	6 (7.0%)
Granulocytopenia	5 (2.9%)	1 (1.2%)
Infections and infestations	60 (34.7%)	24 (27.9%)
Pneumonia	22 (12.7%)	7 (8.1%)
Sepsis	12 (6.9%)	1 (1.2%)
Pneumocystis jirovecii pneumonia	8 (4.6%)	0
Lower respiratory tract infection	4 (2.3%)	2 (2.3%)
Neutropenic sepsis	4 (2.3%)	2 (2.3%)
Urinary tract infection	6 (3.5%)	0
Bronchitis	5 (2.9%)	0
Lung infection	4 (2.3%)	1 (1.2%)
Septic shock	4 (2.3%)	1 (1.2%)
Respiratory tract infection	2 (1.2%)	2 (2.3%)
Progressive multifocal leukoencephalopathy	0	2 (2.3%)
Gastrointestinal disorders	49 (28.3%)	5 (5.8%)
Diarrhoea	30 (17.3%)	1 (1.2%)
Colitis	10 (5.8%)	0
Abdominal pain	5 (2.9%)	0
Investigations	40 (23.1%)	4 (4.7%)
Alanine aminotransferase increased	14 (8.1%)	0
Neutrophil count decreased	11 (6.4%)	2 (2.3%)
Aspartate aminotransferase increased	6 (3.5%)	0
Platelet count decreased	4 (2.3%)	1 (1.2%)
White blood cell count decreased	4 (2.3%)	0
Metabolism and nutrition disorders	36 (20.8%)	5 (5.8%)
Hypokalaemia	11 (6.4%)	1 (1.2%)
Hyponatraemia	7 (4.0%)	0
Dehydration	6 (3.5%)	0
Hyperglycaemia	5 (2.9%)	0
Respiratory, thoracic and mediastinal disorders	33 (19.1%)	4 (4.7%)
Dyspnoea	7 (4.0%)	1 (1.2%)
Pneumonitis	8 (4.6%)	0
Respiratory failure	4 (2.3%)	1 (1.2%)
General disorders and administration site conditions	26 (15.0%)	8 (9.3%)
Pyrexia	12 (6.9%)	2 (2.3%)
Fatigue	6 (3.5%)	4 (4.7%)
Asthenia	5 (2.9%)	1 (1.2%)
Vascular disorders	11 (6.4%)	2 (2.3%)
Hypotension	7 (4.0%)	1 (1.2%)
Musculoskeletal and connective tissue disorders	10 (5.8%)	1 (1.2%)
Pain in extremity	4 (2.3%)	0
Skin and subcutaneous tissue disorders	9 (5.2%)	2 (2.3%)
Rash maculo-papular	4 (2.3%)	0
Renal and urinary disorders	9 (5.2%)	1 (1.2%)
Renal failure acute	4 (2.3%)	0
Injury, poisoning and procedural complications	6 (3.5%)	4 (4.7%)
Infusion related reaction	4 (2.3%)	1 (1.2%)

Adverse Events by Relationship to Ofatumumab

The most frequently reported AEs assessed by the investigator as related to ofatumumab were as follows:

- idelalisib + ofatumumab: fatigue (15.0%, 26 subjects), neutropenia (25.4%, 44 subjects), and pyrexia (9.8%, 17 subjects)
- ofatumumab: fatigue and neutropenia (each 12.8%, 11 subjects), and asthenia, chills, and nausea (each 8.1%, 7 subjects)

The most frequently reported ≥Grade 3 AEs assessed by the investigator as related to ofatumumab were as follows:

- idelalisib + ofatumumab: neutropenia (23.1%, 40 subjects), febrile neutropenia (6.4%, 11 subjects), and neutrophil count decreased (4.0%, 7 subjects)
- ofatumumab: neutropenia (11.6%, 10 subjects) and anemia (3.5%, 3 subjects). All other ≥Grade 3 AEs assessed by the investigator as related to ofatumumab occurred in 2 or fewer subjects

Adverse Events of Interest

This section provides information for the following AEs: diarrhoea and/or colitis, rash, pneumonitis, pneumonia, bowel perforation, anaphylaxis, PML, and Richter's transformation and second malignancies.

Table 39: Incidence of Adverse Events of Interest by Time Interval (Safety Analysis Set) - Study GS-US-312-0119

	0 to 12 Weeks		12 to 24 Weeks		> 24 Weeks	
Adverse Event, n (%)	Id + O (N = 173)	O (N = 86)	Id + O (N = 164)	O (N = 58)	Id + O (N = 144)	O (N = 40)
≥ Grade 3 Diarrhea/Colitis	9/173 (5.2)	1/86 (1.2)	7/164 (4.3)	0	24/144 (16.7)	0
≥ Grade 3 Pneumonia	13/173 (7.5)	6/86 (7.0)	6/164 (3.7)	4/58 (6.9)	14/144 (9.7%)	0
All Grades Pneumonitis[a]	7/173 (4.0)	0	3/164 (1.8)	0	2/144 (1.4%)	0
≥ Grade 3 Rash per MST	4/173 (2.3)	2/86 (2.3)	2/164 (1.2)	0	2/144 (1.4%)	0

Table 40: Prevalence of Adverse Events of Interest by Time Interval (Safety Analysis Set) - Study GS-US-312-0119

	0 to 12 Weeks		12 to 24 Weeks		> 24 Weeks	
Adverse Event, n (%)	Id + O (N = 173)	O (N = 86)	Id + O (N = 164)	O (N = 58)	Id + O (N = 144)	O (N = 40)
≥ Grade 3 Diarrhea/Colitis	9/173 (5.2)	1/86 (1.2)	8/164 (4.9)	0	26/144 (18.1)	0
≥ Grade 3 Pneumonia	13/173 (7.5)	6/86 (7.0)	8/164 (4.9)	4/58 (6.9)	15/144 (10.4%)	0
All Grades Pneumonitis[a]	7/173 (4.0)	0	6/164 (3.7)	0	3/144 (2.1%)	0
≥ Grade 3 Rash per MST	4/173 (2.3)	2/86 (2.3)	3/164 (1.8)	0	3/144 (2.1%)	0

Diarrhoea/Colitis

Diarrhoea has been previously observed with idelalisib in clinical studies, and cases of ≥Grade 3 diarrhoea and or colitis have been reported. In the majority of such cases, regardless of the PT reported, subjects presented after several months of idelalisib administration with several weeks of high-volume watery diarrhoea poorly responsive to antidiarrhoeals or to empiric treatment with antimicrobials. Of the 35 subjects in the idelalisib + ofatumumab group, 21 subjects were rechallenged with idelalisib after dose interruption; 10 of these had successful rechallenge at a reduced dose or that starting dose, and 11 had recurrence of the event after rechallenge. The median (Q1, Q3) time to

onset of the first Grade 3 event of diarrhoea/colitis (N = 35) was 30.1 (11.9, 48.4) weeks, and the median (Q1, Q3) time to resolution of highest grade diarrhoea/colitis (N = 29) was 1.7 (1.1, 4.4) weeks. Eleven subjects in the idelalisib + ofatumumab group discontinued idelalisib due to diarrhoea and 3 others discontinued due to colitis; the events resolved following study drug discontinuation and prior to the database cutoff date for this report in 10 of these 14 subjects. No deaths due to diarrhoea or colitis were reported.

Rash

Rash was defined per Gilead Medical Search Term (MST), including dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo papular, rash papular, rash prutitic, rash morbiliform, and exfoliative rash. Through the database cutoff date, 28.3% (49 subjects) of the idelalisib + ofatumumab group had rash (per MST) of any grade, and 4.0% (7 subjects) had rash MST of Grade 3 in severity. In the ofatumumab group, 10.5% (9 subjects) had rash, and the event was of Grade 3 severity in 2.3% (2 subjects). The median (Q1, Q3) time to onset of the first Grade 3 event of rash MST (N = 7) was 10.9 (5.7, 47.1) weeks in the idelalisib + ofatumumab group; in the 2 subjects with Grade 3 rash MST in the ofatumumab alone group, the times to onset were 0.1 and 3.0 weeks.

There were no Grade 4 (ie, life-threatening) events of rash in either treatment group. In the idelalisib + ofatumumab group, 3 subjects (1.7%) discontinued idelalisib due to 1 of the rash MST terms.

Pneumonitis

Pneumonitis has been reported previously in subjects who have received idelalisib. Through the database cutoff date for this report, 6.4% (11 subjects) of the idelalisib + ofatumumab group had pneumonitis of any grade (including 1 subject, Subject [redacted], with the verbatim term "interstitial pneumonitis" [Grade 2] that was coded to the PT "interstitial lung disease" per MedDRA coding convention, and 4.6% (8 subjects) had pneumonitis of ≥Grade 3 in severity. In the ofatumumab group, no subjects had pneumonitis.

Five subjects in the idelalisib + ofatumumab group discontinued idelalisib due to pneumonitis and the events resolved following study drug discontinuation and prior to the database cutoff date for this report in 2 of these 5 subjects.

Overall, there was 1 death due to pneumonitis in a subject (Subject [redacted]) with history of emphysema and past chemoimmunotherapy including chlorambucil, fludarabine, bendamustine and rituximab who was initially admitted for treatment of chest x-ray findings of bilateral lower lobe pneumonia.

Pneumonia

For the purposes of this analysis, "pneumonia" included the PTs pneumonia, lung infection, lung infiltration, pneumocystis jiroveci pneumonia, pneumonia legionella, lung infection pseudomonal, pneumonia fungal, respiratory tract infection, lower respiratory tract infection, and lower respiratory tract infection bacterial. Through the database cutoff date, 24.9% (43 subjects) of the idelalisib + ofatumumab group had an AE of pneumonia (any grade), and 17.9% (31 subjects) had events that were ≥Grade 3 in severity (26 subjects with Grade 3, 4 subjects with Grade 4, and 1 subject with Grade 5). In the ofatumumab group, 17.4% (15 subjects) had pneumonia of any grade, and 10.5% (9 subjects had events that were ≥Grade 3 in severity (7 subjects with Grade 3 and 2 subjects with Grade 5). The median (Q1, Q3) time to onset of the first ≥Grade 3 event of pneumonia was 17.6 (4.1, 33.1) weeks in the idelalisib + ofatumumab group (N = 31) and was 7.6 (1.9, 16.9) weeks in the ofatumumab alone group.

Seven subjects in the idelalisib + ofatumumab group discontinued study drug due to pneumonia.

Bowel Perforations

Bowel perforations have been reported in a few subjects who have received idelalisib in other clinical trials. Through the database cutoff date for this report, 1 subject (0.6%) in the idelalisib + ofatumumab group had an AE of large intestine perforation, compared with no subjects in the ofatumumab alone group. This subject died of septic shock secondary to intestinal tumor perforation, as an autopsy revealed a perforated mucinous adenocarcinoma of the large intestine.

Anaphylaxis

Anaphylaxis has been reported previously in a few subjects who have received idelalisib in other clinical trials. Through the database cutoff, events in the HLT of anaphylactic responses were reported for no subjects in the idelalisib + ofatumumab group, compared with 1 subject (1.2%) of the ofatumumab alone group.

Progressive Multifocal Leukoencephalopathy

PML has been reported previously in Study GS-US-312-0116, in 1 subject who received idelalisib in combination with rituximab. In Study GS-US-312-0119 through the database cutoff date, no subjects in the idelalisib + ofatumumab group had an AE of PML, compared with 2 subjects (2.3%) of the ofatumumab alone group.

Richter's Transformation / Second Malignancies

The incidence on the Richter's transformation and second malignancies is presented inTable 41.

Table 41: Richter's transformation and second malignancies adjusted for exposure (Safety Analysis Set) - Study GS-US-312-0119

	Id + O (N = 173)			O (N = 86)		
Preferred Term	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)
Richter's transformation	5	172.8	0.03 (0.0094, 0.0675)	4	32.8	0.12 (0.0333, 0.3125)
Second malignancies	24	159.4	0.15 (0.0964, 0.2240)	8	30.4	0.26 (0.1136, 0.5183)

CI = confidence interval; Id = idelalisib; O = ofatumumab
AEs were classified by PTs using MedDRA version 17.1.

a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

Source: Section 15.1, Table 3.1.25

Serious adverse event / deaths / other significant events

Idelalisib-related SAEs were reported for 42.2% (73 subjects) of the idelalisib + ofatumumab group. The most common events considered related to idelalisb were diarrhoea (8.7%, 15 subjects), febrile neutropenia (6.9%, 12 subjects), pneumonia, and pyrexia (each reported in 5.2%, 9 subjects).

Table 42: SAEs reported for at least 2% of subjects considered related to idelalisib (ITT analysis set) – Study GS-US-312-0119

System Organ Class Preferred Term	Id + O (N = 173)
Number of Subjects (%) with SAEs Related to Idelalisib	73 (42.2)
Diarrhoea	15 (8.7)
Febrile neutropenia	12 (6.9)
Pneumonia	9 (5.2)
Pyrexia	9 (5.2)
Colitis	8 (4.6)
Pneumonitis	8 (4.6)[a]
Neutropenia	6 (3.5)
Neutrophil count decreased	6 (3.5)
Pneumocystis jirovecii pneumonia	5 (2.9)
Sepsis	5 (2.9)

Id = idelalisib; O = ofatumumab; SAE = serious adverse event
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT were counted once per PT.

a Includes 1 event (in Subject [redacted]) with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease."

Idelalisib-related SAEs were reported for 42.2% (73 subjects) of the idelalisib + ofatumumab group. SAEs assessed by the investigator as related to idelalisib that occurred in more than 2% of subjects. The most common events considered related to idelalisb were diarrhoea (8.7%, 15 subjects), febrile neutropenia (6.9%, 12 subjects), pneumonia, and pyrexia (each reported in 5.2%, 9 subjects).

Serious AEs considered related to ofatumumab were reported for 22.5% (39 subjects) of the idelalisib + ofatumumab group and 19.8% (17 subjects) of the ofatumumab group. The most frequently reported SAEs considered related to ofatumumab were as follows:

- idelalisib + ofatumumab: febrile neutropenia (5.2%, 9 subjects), pneumonia and neutropenia (each 2.9%, 5 subjects), and pyrexia and neutrophil count decreased (each 2.3%, 4 subjects)
- ofatumumab alone: All SAEs related to ofatumumab occurred in 2 or fewer subjects.

Table 43: SAEs reported for at least 2% of subjects in either treatment group (ITT Analysis Set) - Study GS-US-312-0119

System Organ Class Preferred Term	Id + O (N = 173)	O (N = 86)
Number of Subjects (%) with any SAE	121 (69.9)	36 (41.9)
Pneumonia	20 (11.6)	9 (10.5)
Febrile neutropenia	20 (11.6)	3 (3.5)
Pyrexia	19 (11.0)	1 (1.2)
Diarrhoea	17 (9.8)	0
Neutropenia	13 (7.5)	2 (2.3)
Sepsis	11 (6.4)	1 (1.2)
Anaemia	7 (4.0)	2 (2.3)
Colitis	9 (5.2)	0
Pneumonitis	8 (4.6)[a]	0
Thrombocytopenia	5 (2.9)	2 (2.3)
Urinary tract infection	7 (4.0)	0
Hypotension	5 (2.9)	1 (1.2)
Neutropenic sepsis	4 (2.3)	2 (2.3)
Neutrophil count decreased	6 (3.5)	0
Pneumocystis jirovecii pneumonia	6 (3.5)	0
Abdominal pain	4 (2.3)	1 (1.2)
Atrial fibrillation	3 (1.7)	2 (2.3)
Lower respiratory tract infection	3 (1.7)	2 (2.3)
Respiratory tract infection	3 (1.7)	2 (2.3)
Septic shock	4 (2.3)	1 (1.2)
Bronchitis	4 (2.3)	0
Dehydration	4 (2.3)	0
Dyspnoea	4 (2.3)	0
Lung infection	4 (2.3)	0
Nausea	4 (2.3)	0
Vomiting	4 (2.3)	0
Progressive multifocal leukoencephalopathy	0	2 (2.3)

Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT were counted once per PT.
a Includes 1 event (in Subject [redacted]) with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease."
Source: Section 15.1, Tables 3.1.9 and 3.1.18

Deaths

Sixty-three subjects died, 37 during the study (through 30 days after the last dose of study medication). In the idelalisib + ofatumumab group, 23.7% (41 subjects) died, 16.8% (29 subjects) on study and 6.9% (12 subjects) during long-term follow-up (defined as later than the end of study + 30 days). In the ofatumumab alone group, 25.6% (22 subjects) died, 9.3% (8 subjects) on study and 16.3% (14 subjects) during long-term follow-up.

The most common events leading to death were septic shock (1.7% [3 subjects] of the idelalisib + ofatumumab group and 1.2% [1 subject] of the ofatumumab alone group), pneumonia (0.6% [1 subject] of the idelalisib + ofatumumab group and 2.3% [2 subjects] of the ofatumumab alone group), and sepsis (1.7% [3 subjects] of the idelalisib + ofatumumab group and 0 subjects in the ofatumumab alone group).

A summary of the coded TEAEs leading to death as of the data cutoff of 01 Sep 2015 is shown in the next table. The most common MedDRA System Organ Class (SOC) leading to death was Infections and Infestations (occurring in 6.9% of subjects in the idelalisib + ofatumumab group and 5.8% of subjects in the ofatumumab alone group).

The second most common SOC leading to death was Cardiac Disorders.

Table 44: Adverse Events Leading to Death by Decreasing SOC and PT - GS-US-312-0119 (Safety Analysis Set) 01 Sep 2015 Data Cutoff

Adverse Events by System Organ Class and Preferred Term	Id + O (N = 173) n (%)	O (N = 86) n (%)
Subjects with TEAEs Leading to Death	22 (12.7)	6 (7.0)
Infections and Infestations	12 (6.9)	5 (5.8)
Septic shock	4 (2.3)	1 (1.2)
Pneumonia	3 (1.7)	2 (2.3)
Sepsis	3 (1.7)	0
Progressive multifocal leukoencephalopathy	0	2 (2.3)
Viral sepsis	1 (0.6)	0
Candida sepsis	1 (0.6)	0
Respiratory tract infection	1 (0.6)	0
Cardiac Disorders	7 (4.0)	0
Cardiogenic shock	2 (1.2)	0
Cardiac failure	1 (0.6)	0
Acute myocardial infarction	1 (0.6)	0
Myocardial infarction	1 (0.6)	0
Arrhythmia	1 (0.6)	0
Atrial fibrillation	1 (0.6)	0
Cardiac arrest	1 (0.6)	0
Respiratory, Thoracic, and Mediastinal Disorders	3 (1.7)	1 (1.2)
Chronic obstructive pulmonary disease	1 (0.6)	0
Pneumonitis	1 (0.6)	0
Pulmonary fibrosis	1 (0.6)	0
Respiratory failure	0	1 (1.2)
Blood and Lymphatic System Disorders	1 (0.6)	0
Thrombocytopenia	1 (0.6)	0
General Disorders and Administration Site Conditions	1 (0.6)	0
Death	1 (0.6)	0
Nervous System Disorders	0	1 (1.2)
Central Nervous System Leukemia	0	1 (1.2)

Focusing on Cardiac-related TEAEs the percentage of some TEAEs leading to death was higher in the idelalisib + ofatumumab group compared to the ofatumumab alone group (cardiac disorders: 4.0% in the idelalisib + ofatumumab group vs 0% in the ofatumumab alone group). For specific cardiac events, TEAEs leading to death are shown in Table 45

Table 45: TEAEs Leading to Death by SOC, HLT, and PT - Study GS-US-312-0119 (Safety Analysis Set)

	Id + O (N = 174) n (%)	O (N = 87) n (%)
Number of Subjects with Any TEAEs Leading to Death	22 (12.7)	6 (7.0)
Cardiac Disorders	7 (4.0)	0
Heart Failures NEC	3 (1.7)	0
Cardiogenic Shock	2 (1.2)	0
Cardiac Failure	1 (0.6)	0
Ischaemic Coronary Artery Disorders	2 (1.2)	0
Acute Myocardial Infarction	1 (0.6)	0
Myocardial Infarction	1 (0.6)	0
Rate and Rhythm Disorders NEC	1 (0.6)	0
Arrhythmia	1 (0.6)	0
Supraventricular Arrhythmias	1 (0.6)	0
Atrial Fibrillation	1 (0.6)	0
Ventricular Arrhythmias and Cardiac Arrest	1 (0.6)	0
Cardiac Arrest	1 (0.6)	0
Respiratory Failure	0	1 (1.2)

Table 46: TEAEs Leading to Death by SOC, HLT, and PT in Randomized, Controlled CLL Studies of Idelalisib + Anti-CD20 Therapy - Studies GS-US-312-0116 and GS-US-312-0119 (Safety Analysis Set)

	Id + Anti-CD20 (N = 283) n (%)	Anti-CD20 (N = 194) n (%)
Number of Subjects with Any TEAE Leading to Death	22 (7.8)	17 (8.8)
Cardiac Disorders	6 (2.1)	2 (1.0)
Heart Failures NEC	3 (1.1)	1 (0.5)
Cardiac Failure	1 (0.4)	1 (0.5)
Cardiogenic Shock	2 (0.7)	0
Ischaemic Coronary Artery Disorders	2 (0.7)	0
Acute Myocardial Infarction	1 (0.4)	0
Myocardial Infarction	1 (0.4)	0

Left Ventricular Failures	0	1 (0.5)
Left Ventricular Failure	0	1 (0.5)
Rate and Rhythm Disorders NEC	1 (0.4)	0
Arrhythmia	1 (0.4)	0
Supraventricular Arrhythmias	1 (0.4)	0
Atrial Fibrillation	1 (0.4)	0

Laboratory findings

A summary of haematology abnormalities and serum chemistry abnormalities are presented in Table 47 and Table 48.

Table 47: Summary of treatment-emergent haematology abnormalities (Safety Analysis Set) - Study GS-US-312-0119

Parameter[a]	Id + O (N = 173)	O (N = 86)
Hemoglobin decreased		
Any Grade	74 (42.8)	34 (39.5)
≥ Grade 3	30 (17.3)	10 (11.6)
Lymphocyte count increased		
Any Grade	31 (17.9)	5 (5.8)
≥ Grade 3	18 (10.4)	3 (3.5)
Lymphocyte count decreased		
Any Grade	35 (20.2)	19 (22.1)
≥ Grade 3	18 (10.4)	9 (10.5)
Neutrophil count decreased		
Any Grade	122 (70.5)	50 (58.1)
≥ Grade 3	82 (47.4)	28 (32.6)
Platelet count decreased		
Any Grade	58 (33.5)	21 (24.4)
≥ Grade 3	23 (13.3)	10 (11.6)
Leukocytes (white blood cell decreased)		
Any Grade	69 (39.9)	32 (37.2)
≥ Grade 3	24 (13.9)	10 (11.6)

Id = idelalisib; O = ofatumumab
The Safety Analysis Set included all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Grades were obtained per CTCAE version 4.03.

a Worst grade at post baseline

Source: Section 15.1, Table 3.2.2

Table 48: Summary of treatment-emergent serum chemistry abnormalities: events with any occurrence of ≥Grade 3 severity (Safety Analysis Set) - Study GS-US-312-0119

Parameter[a]	Id + O (N = 173)	O (N = 86)
Albumin decreased		
Any Grade	52 (30.1)	17 (19.8)
≥ Grade 3	3 (1.7)	1 (1.2)
Alkaline phosphatase increased		
Any Grade	43 (24.9)	13 (15.1)
≥ Grade 3	3 (1.7)	1 (1.2)
ALT increased		
Any Grade	90 (52.0)	18 (20.9)
≥ Grade 3	20 (11.6)	1 (1.2)
AST increased		
Any Grade	61 (35.3)	17 (19.8)
≥ Grade 3	14 (8.1)	1 (1.2)
Bilirubin increased		
Any Grade	26 (15.0)	7 (8.1)
≥ Grade 3	2 (1.2)	0
Albumin-corrected calcium increased		
Any Grade	21 (12.1)	8 (9.3)
≥ Grade 3	3 (1.7)	1 (1.2)
Creatinine increased		
Any Grade	22 (12.7)	13 (15.1)
≥ Grade 3	2 (1.2)	0
Creatinine clearance decreased		
Any Grade	33 (19.1)	12 (14.0)
≥ Grade 3	5 (2.9)	3 (3.5)
GGT increased		
Any Grade	69 (39.9)	17 (19.8)
≥ Grade 3	7 (4.0)	0
Glucose increased		
Any Grade	104 (60.1)	48 (55.8)
≥ Grade 3	21 (12.1)	4 (4.7)
Potassium increased		
Any Grade	4 (2.3)	3 (3.5)
≥ Grade 3	2 (1.2)	1 (1.2)
Potassium decreased		
Any Grade	36 (20.8)	8 (9.3)
≥ Grade 3	10 (5.8)	2 (2.3)
Phosphate decreased		
Any Grade	29 (16.8)	3 (3.5)
≥ Grade 3	14 (8.1)	1 (1.2)
Sodium decreased		
Any Grade	43 (24.9)	19 (22.1)
≥ Grade 3	12 (6.9)	3 (3.5)
Triglycerides increased		
Any Grade	102 (59.0)	45 (52.3)
≥ Grade 3	12 (6.9)	2 (2.3)
Urate increased		
Any Grade	19 (11.0)	6 (7.0)
≥ Grade 3	3 (1.7)	0

Id = idelalisib; O = ofatumumab
The Safety Analysis Set included all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Grades were obtained per CTCAE version 4.03.
a Worst grade at post baseline

The rates of abnormalities (all grades) adjusted for exposure time in respective arm were generally either similar in the 2 groups or higher in the ofatumumab alone group, with the exception of ALT increases. There was also greater treatment-adjusted incidence of increased cholesterol, although the highest treatment-emergent cholesterol abnormalities were Grade 2.

Safety in special populations

The MAH did not submit data on safety in special populations. However, they have submitted the incidence of certain AEs by age groups.

Table 49: Incidence of Certain AEs by Age Group - Studies GS US 312 0116 and GS US 312 0119 (Safety Analysis Set)

MedDRA Term	Age < 65 N = 416 n (%)[1]	Age 65 – 74 N = 444 n (%)[1]	Age 75 – 84 N = 194 n (%)[1]	Age ≥ 85 N = 19 n (%)[1]
Total ADRs	326 (78.4)	345 (77.7)	152 (78.4)	12 (63.2)
Serious ADRs – Total	120 (28.8)	146 (32.9)	78 (40.2)	4 (21.1)
Fatal	10 (2.4)	15 (3.4)	6 (3.1)	0
Hospitalization/prolong existing hospitalization	102 (24.5)	126 (28.4)	66 (34.0)	4 (21.1)
Life-threatening	4 (1.0)	7 (1.6)	6 (3.1)	0
Disability/incapacity	8 (1.9)	6 (1.4)	0	0
Other (medically significant)	25 (6.0)	44 (9.9)	28 (14.4)	1 (5.3)
AE leading to drop-out	73 (17.5)	95 (21.4)	55 (28.4)	4 (21.1)
Psychiatric disorders (SOC)	16 (3.8)	16 (3.6)	3 (1.5)	1 (5.3)
Nervous system disorders (SOC)	64 (15.4)	49 (11.0)	29 (14.9)	1 (5.3)
Accidents and injuries (SMQ)	2 (0.5)	1 (0.2)	2 (1.0)	0
Cardiac disorders (SOC)	8 (1.9)	6 (1.4)	4 (2.1)	0
Vascular disorders (SOC)	19 (4.6)	17 (3.8)	9 (4.6)	1 (5.3)
Cerebrovascular disorders (SMQ)	0	1 (0.2)	1 (0.5)	0
Infections and infestations (SOC)	101 (24.3)	96 (21.6)	48 (24.7)	1 (5.3)
Quality of life decreased (PT)	0	0	0	0
Sum of Postural Hypotension, Falls, Black outs, Syncope, Dizziness, Ataxia, Fractures	15 (3.6)	7 (1.6)	8 (4.1)	0

1 Cumulative number over all indications in the clinical trial programme and percentage over the age group.
The Safety Analysis Set includes all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Adverse Drug Reactions (ADRs) include treatment-emergent AEs assessed by the investigator as related to treatment with idelalisib.
Serious criteria were not captured on case report forms; therefore, serious ADRs were collected from the Gilead safety database.
Serious ADRs include all SAEs assessed by the investigator as related to treatment with idelalisib.
Source: Table CHMP.4

Safety related to drug-drug interactions and other interactions

The MAH did not submit data on safety on drug-drug interactions.

Discontinuation due to adverse events

A summary of all AEs that led to discontinuation of idelalisib is presented in Table 50 and by subject in Table 51.

Table 50: AEs leading to idelalisib discontinuation in >2% of subjects (ITT analysis) – Study GS-US-312-0119

System Organ Class Preferred Term	Id + O (N = 173)
Number of Subjects (%) with AEs Leading to Idelalisib Discontinuation[a]	53 (30.6)
Gastrointestinal Disorders	15 (8.7%)
Diarrhea	11 (6.4%)
Infections and Infestations	12 (6.9%)
Pneumonia	5 (2.9)
Respiratory, thoracic, and mediastinal disorders	7 (4.0)
Pneumonitis	5 (2.9)[b]
Investigations	6 (3.5)
Alanine aminotransferase increased	4 (2.3)

AE = adverse event; Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT were counted once per PT.

a Four subjects ([redacted]) had AEs with a study drug action taken of "drug withdrawn," but had other reasons given by the physician for idelalisib withdrawal on the drug discontinuation eCRF (physician decision, withdrawal by subject, progressive disease, and death, respectively).

b Includes 1 event (in Subject [redacted]) with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease."

The most common AE leading to ofatumumab discontinuation was pneumonia, occurring in 1.7% (3 subjects) of the idelalisib + ofatumumab group and 3.5% (3 subjects) of the ofatumumab alone group. All other AEs leading to discontinuation of ofatumumab occurred in 2% or less of either treatment group.

Table 51: Summary of proportion of patients with dose modification and interruption for idelalisib exposure (Safety Analysis Set) - Study GS-US-312-0119

	Id + O (N = 173)
Subjects with No Dose Modification, n (%)	80 (46.2)
Subjects with Dose Modification, n (%)	93 (53.8)
Subjects with Dose Interruption	90 (52.0)
Subjects with Dose Rechallenged	89 (51.4)
Subjects Rechallenged at 150 mg	65 (37.6)
Subjects Rechallenged at 100 mg	24 (13.9)
Subjects With Dose Re-escalation	7 (4.0)
Subjects with Dose Reduction Without Interruption	3 (1.7)
Subjects with Dose Re-escalated	0
Modification due to AE	76 (43.9)
Modification due to Other[c]	5 (2.9)
Modification due to AE and Other	12 (6.9)

AE = adverse event; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation

a Duration of exposure (months) = (min (last idelalisib dosing date as captured on study drug completion eCRF page, data cutoff date) first idelalisib 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.

c Reasons included "Team was concerned that transfusion requirements were due to progressive disease," "Post-operative healing," "By mistake, suspicion of PD," "Patient received other anti-cancer treatment/radiotherapy for SCC on face," and "Indeterminated bone marrow aplasia." (Appendix 16.2, Listing 1.10.1)

Source: Section 15.1, Tables 1.11 and 1.13

The proportion of subjects with a delay in ofatumumab administration due to treatment emergent AEs were ~55% and 50 % in the experimental and control arm, respectively. The most common event resulting in ofatumumab delay was infusion-related reaction, occurring in 10.4% (18 subjects) of the idelalisib + ofatumumab group and 23.3% (20 subjects) of the ofatumumab alone group. Neutropenia was the second most common reason (12.1% [21 subjects] of the idelalisib + ofatumumab group and 4.7% [4 subjects] of the ofatumumab alone group), followed by pneumonia (1.7% [3 subjects] of the idelalisib + ofatumumab group and 8.1% [7 subjects] of the ofatumumab alone group).

2.5.1. Discussion on clinical safety

As the treatment duration with ofatumumab was limited to ~5 months, whereas idelalisib was dosed continuously, there is an imbalance in the exposure time observed between the two treatments and hence, the adjustment to exposure time does not seem to be justified. In addition, the dose of ofatumumab in the control arm was higher (2000 mg per infusion except for the first infusion of 300 mg in both arms) as compared to the experimental arm (idelalisib + ofatumumab 1000 mg), which affects comparability of the 2 arms and compromises attribution of causal relations to safety events.

In general, the safety findings of idelalisib combined with ofatumumab in study GS-US-312-0119 seem to be consistent with the previously known safety profile of idelalisib, both in monotherapy and when combined with rituximab in previously treated CLL patients. Elevations in hepatic transaminases are among the most frequent AEs encountered but are generally moderate and most often self-limiting, without necessitating interruption of treatment. Severe cases of drug-induced liver toxicity, fulfilling Hy's law, are as yet rarely reported. Other AEs that are frequently reported during idelalisib treatment include diarrhoea, rash, pneumonitis and infections eg pneumonia. These AEs are often more severe and require dose interruption, dose reductions, and sometimes permanent discontinuation of idelalisib.

The incidence of infections could be related to neutropenia, which is often reported in CLL patients treated with idelalisib.

A higher frequency of on study deaths due to causes other than progressive disease 27/173 (15.6%) in the idelalisib+ofatumumab arm vs 5/86 (5.8%) and a higher rate of deaths due to TEAEs (12.7% vs 7.0%) was observed and raised some concern. The CHMP requested the MAH to present all TEAEs leading to death, in relation to time on treatment and in relation to which treatment was being received at the time of death. The MAH presented several analyses with study GS-US-312-0119 and pooled with study GS-US-312-0116 and for TEAEs leading to death and cardiac-related TEAEs leading to death (15 January 2015 data cut). The data showed no consistent safety signals with regard to TEAEs leading to death and cardiac-related events leading to death have emerged on analysis of the idelalisib clinical development program.

Rituximab and ofatumumab have not yet been directly compared in clinical studies in CLL and their relative tolerability/toxicity has not been evaluated. Tolerability of the combined regimen in this study does appear somewhat more limited than that in study GS-US-312-0119 (eg. discontinuation of idelalisib in this study was 30.6% compared to 17.3% in study GS-US-312-0116), but comparisons are hampered by the different length of follow-up. The MAH presented data comparing the incidence of the key safety findings in the 2 studies but no important differences were observed.

2.5.2. Conclusions on clinical safety

No new ADRs have been reported in study GS-US-312-0119 with the combination of idelalisib+ofatumumab. The ADRs and frequency reported were comparable with what has been previously described and were considered well tolerated and manageable. Therefore, the safety and tolerability of idelalisib in combination with ofatumumab is considered acceptable.

2.6. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from emerging from post-marketing data

During the decision making process, the European Commission (EC) was informed of new safety data from ongoing clinical trials of an increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups. This important safety signals had been observed in three clinical trials by the Independent Safety Data Monitoring group overseeing the studies. The trials evaluated treatment combinations with chemotherapy and immunotherapy which are currently not authorised for Zydelig (idelalisib) in populations with earlier disease characteristics than the currently approved indication. However, in light of the emerging safety data, the EC considered that the findings from the clinical trials and all available safety data related to idelalisib should be reviewed in order to assess their potential impact on the benefit-risk balance of Zydelig in the approved indications and relevant ongoing variations.

Therefore, on 11 March 2016, the EC triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Zydelig (idelalisib) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The MAH submitted data from all relevant clinical studies, including the pivotal studies supporting the initial marketing authorisation and extension of indication in combination with ofatumumab as well as studies that evaluated the safety and efficacy of idelalisib in new treatment combinations and/or study populations (including studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125). Some of

these studies were completed and a final or interim (including completed primary analysis) clinical study report (CSR) was available while for the three most recent the data was interim and therefore limited analyses were available. Temporary measures such as not to initiate idelalisib treatment and provisional risk minimisation measures, update posology and warnings were agreed in the meantime (EC decision 23 March 2016) while the assessment of the emergent safety information was ongoing.

An overview of the most relevant studies submitted as part of the Article 20 is presented in the table below.

Table 52. Overview of key studies submitted

Study ID and design	Population	Treatment
Previously treated CLL		
GS-US-312-0116 (RCT)	CLL*. Relapsed/refractory within at least 24 months of at least one prior treatment (median 3 prior lines of therapy), mean 9 years since diagnosis. Advanced poor prognosis. 95 (43%) patients with 17p deletion/*TP53* mutation.	Idelalisib + rituximab (n=110) / placebo + rituximab (n=110)
GS-US-312-0119 (RCT)	CLL*. Previously treated refractory or relapsed CLL (median 3 prior lines of therapy), mean 8 years since diagnosis. 103 (39%) patients with 17p deletion/*TP53* mutation	Idelalisib + ofatumumab (n=173) / ofatumumab (n=86)
GS-US-312-0115 (RCT)	CLL†. Previously treated relapsed CLL (median 2 prior lines of therapy),mean 7 years since diagnosis.137 (33%) patients with 17p deletion/*TP53* mutation.	Idelalisib + rituximab + bendamustine (n=207) / placebo + rituximab + bendamustine (n=209)
Previously untreated CLL		
GS-US-312-0123 (RCT)	CLL. First line, mean 3.5 years since diagnosis. 38 (12%) patients with 17p deletion/*TP53* mutation.	Idelalisib + rituximab + bendamustine (n=156) / placebo + rituximab + bendamustine (n=154)
101-08 (single arm)	Elderly patients (>65 y) with CLL (n= 59; 5 patients with SLL). First line, mean 4 years since diagnosis. 15 (14%) patients with 17p deletion/*TP53* mutation)	Cohort 1: n=64 idelalisib + rituximab, cohort 2: n=41 idelalisib
Previously treated iNHL		
101-09 (single arm)	Refractory iNHL. Mean 6 years since diagnosis. Median 4 prior lines of therapy	Idelalisib (n=125)
GS-US-313-0124 (RCT)	Previously treated iNHL. Mean 7 years since diagnosis. Median 1 prior lines of therapy	Idelalisib + rituximab (n=198) / placebo + rituximab (n=95)
GS-US-313-0125 (RCT)	Previously treated iNHL. Mean 6.5 years since diagnosis. Median 2 prior lines of therapy	Idelalisib + rituximab + bendamustine (n=317) / placebo + rituximab + bendamustine (n=155)

Efficacy aspects

In the interim results of studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 overall survival was numerically lower in the idelalisib arms.

Table 53. Kaplan Meier of overall survival at 3 months in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125

Study 123 (previously untreated CLL)	**Idelalisib + BR**	**Placebo + BR**
KM of OS at 3 months (95% CI)	96.1 (91.6, 98.2)	100 (NR, NR)
Study 124 (previously treated iNHL)	**Idelalisib + R**	**Placebo + R**
KM of OS at 3 months (95% CI)	97.7 (94, 99.1)	100 (NR, NR)
Study 125 (previously treated iNHL)	**Idelalisib + BR**	**Placebo + BR**
KM of OS at 3 months (95% CI)	97.7 (95.2, 98.9)	99.3 (95.5, 99.9)

The MAH presented the preliminary PFS, OS and best overall response data of a sub-analysis of the 38 first line patients with 17p deletion and/or *TP53* mutation that were included in study GS-US-312-0123.

Table 54. Progression-Free survival and overall survival in subjects with 17p deletion/*TP53* mutation by treatment arm, investigator assessment (Intent to Treat Analysis Set)

	IDL + BR (N = 18)	**Placebo + BR (N = 20)**
Number (%) of Subjects with Events	2 (11.1%)	8 (40.0%)
Disease Progression	0	7 (35.0%)
Death	2 (11.1%)	1 (5.0%)
Number (%) of Subjects Censored	16 (88.9%)	12 (60.0%)
Ongoing	16 (88.9%)	12 (60.0%)
Discontinued Study[a]	0	0
KM of PFS (Months)		
Q1 (95% CI)	NR (0.8, NR)	6.8 (2.3, 10)
Median (95% CI)	NR (NR, NR)	9.5 (6.8, NR)
Q3 (95% CI)	NR (NR, NR)	10 (9.5, NR)
KM of PFS Rate [95% CI]		
At 24 weeks	93.8 (63.2, 99.1)	85 (60.4, 94.9)
At 48 weeks	86.5 (55.8, 96.5)	22.7 (1.2, 61)
Hazard Ratio [95% CI]	0.25 (0.05, 1.20)	
KM of OS (Months)		
Q1 (95% CI)	NR (0.8, NR)	NR (6.6, NR)
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
Q3 (95% CI)	NR (NR, NR)	NR (NR, NR)
KM of OS Rate (95% CI)		
At 3 months	94.4 (66.6, 99.2)	100 (NR, NR)
Hazard Ratio (95% CI)	0.79 (0.13, 4.73)	

Table 55. Best overall response in subjects with 17p deletion/TP53 mutation by treatment arm, investigator assessment (ITT Analysis Set)

	IDL + BR (N = 18)	Placebo + BR (N = 20)
Not evaluable	4 (22.2%)	0
Progressive disease	0	3 (15.0%)
Stable disease	0	5 (25.0%)
Partial response	9 (50.0%)	10 (50.0%)
Complete response	5 (27.8%)	2 (10.0%)

In study GS-US-312-0123 there were no statistically significant differences between the treatment groups for PFS, best overall response or OS in previously untreated CLL subjects with 17p deletion and/or TP53 mutation. However, the immaturity of the data and small number of patients are noted as a plausible reason for the lack of observed benefit. Although the dataset for first line patients with 17p deletion and/or TP53 mutation is too limited to draw direct conclusions, the overall assessment does not challenge the extrapolation of the benefits observed in relapsed/refractory CLL patients with 17p deletion or TP53 mutation to treatment naïve patients, for idelalisib in combination with rituximab or ofatumumab.

Nevertheless, in view of the limited data available in this subset and considering availability of other options for first line treatment for CLL patients, the PRAC was of the view that as a precaution, idelalisib should only be used in patients with 17p deletion or TP53 mutation if they are not eligible for any other therapies.

Safety aspects

Serious infections and deaths

Interim results showed an increase in incidence of deaths and AE leading to deaths in the idelalisib arms compared to placebo for each of the studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125.

Table 56. 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%

In the pooled data from the three studies, Treatment-emergent adverse events (TEAE) leading to death in the idelalisib and placebo arms was predominantly in the system organ class of infections and infestations (2.0% vs 0.7%) and respiratory disorders (1.2% vs 0%).

Due to the first line setting of CLL studies GS-US-312-0123 and 101-08, time since diagnosis was shorter in these patients (see table 3). For iNHL studies, time since initial diagnosis was comparable between treatment and control arms within studies and also across studies. The median number of prior regimens was similar in studies GS-US-313-0124 and GS-US-313-0125 and higher in study 101-09 (see table 3).

In study GS-US-312-0123 the causes of death for 9 of the 12 subjects (75%) on the idelalisib plus bendamustine and rituximab arm were events either directly reported as infectious events (including one case of CMV sepsis and one PJP associated with cardiopulmonary failure) or associated with infection, compared with 2 of 11 subjects (18.2%) on the idelalisib plus rituximab arm in study GS-US-313-0124 and 15 of 28 subjects (53.6%) on the idelalisib plus bendamustine and rituximab arm in study GS-US-313-0125 (including two cases of PJP). In the cases where the cause of death was not associated with infectious aetiologies, it mainly consisted of progressive disease. There was a notable difference in the rates of infection between treatment arm and control arm in study GS-US-313-0124, which was also seen, albeit to a lesser extent, in study GS-US-313-0125.

In CLL studies, GS-US-312-0116, GS-US-312-0119 and GS-US-312-0115 PJP accounted respectively for 5-12 % and 0-4% of serious infection cases in the idelalisib and control arms respectively and cytomegalovirus (CMV) accounted for 0% of the serious infection cases in studies GS-US-312-0116 and GS-US-312-0119 and 7.2% and 6.1% in the idelalisib and control arms of study GS-US-312-0115, respectively. In iNHL studies, PJP cases accounted for 3-10% and CMV for 6-8% of the serious infection cases in the idelalisib arms and both accounted for 0% of serious infection case in the control arms.

Death rates in the single arm study 101-08 were comparable to those observed in the front line setting treatment arm (6.3% and 4.9% in cohort 1 and 2, respectively). Whilst all deaths in study GS-US-312-0116 occurred during treatment, a very large proportion of deaths in study GS-US-312-0119 and GS-US-312-0115 occurred during long term follow-up (12.1% and 9.2% respectively). Broken down by time periods ≤1, >1-≤2, >2-≤3, >3-≤6 and >6 months and adjusted for the number of patients at risk, the death rates for each periods in first line CLL were 1.9%, 0.7%, 1.4%, 2.1% and 1.5% respectively compared to 1.9%, 1.0%, 1.0%, 3.0% and 19.7%, respectively in relapsed/refractory patients.

There was no apparent relationship between treatment duration and risk of infectious SAE.

The PRAC reviewed the safety data from studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 in the context of the results from other studies. The infectious SAE rate in the idelalisib + rituximab + bendamustine arm in treatment naïve patients was comparable or slightly lower than rates in the relapsed/refractory CLL studies where idelalisib was administered in combination with rituximab, ofatumumab or rituximab and bendamustine. However, it was noted that the rate of infectious SAEs in the control arms the studies presented was much lower compared to that in the other previous CLL studies. Analyses suggest that treatment with idelalisib in CLL versus placebo in combination with rituximab, ofatumumab or bendamustine and rituximab, results in a higher incidence of early infections across all quartiles of treatment-free intervals. There was no clear relationship between risk of infection and deaths and number of prior therapies or time off treatment prior to idelalisib initiation or between first line and relapsed/refractory patients.

The PRAC considered that risk minimisation measures were warranted in order to bring the use in clinical practice closer to that in the clinical trials where a positive benefit-risk was observed. Patients should not start taking idelalisib in case of systemic bacterial, fungal or viral infection and that patients should be monitored for respiratory signs and symptoms throughout treatment and advised to report promptly any new respiratory symptoms. Further, as neutropenia leads to a higher risk of infection and infections were reported from the first month in the study, in line with measures applied in clinical trials and as implemented in the provisional measures, blood counts should be monitored every two weeks during the first six months of treatment. Blood counts monitoring should be intensified to weekly in patients with absolute neutrophil counts (ANC) below 1,000 per mm^3 and treatment withheld while ANC is below 500 per mm^3. Treatment may then be restarted at a reduced dose of 100 mg twice daily. In addition, it should be further specified in a footnote to the tabulated list of adverse reactions that the serious infections reported included opportunistic infections as well as bacterial and viral infections such as pneumonia, bronchitis, and sepsis.

- ***Pneumocystis jirovecii* pneumonia**

An increased incidence of PJP cases was observed in the treatment arms compared to the controls in the CLL and iNHL studies. The majority of cases (66% [23/35]) occurred within the first 6 months of treatment, however, while more cases occurred during the first 6 months on treatment, considering the proportion of cases occurring later it was not considered appropriate to limit the administration of PJP prophylaxis to this fixed time window.

Overall, there was no clear relationship to treatment duration or number of prior regimen. The PRAC was of the view that section 4.4 of the SmPC should advise physicians that prophylaxis for PJP should therefore be administered to all patients throughout idelalisib treatment, and for a period of 2 to 6 months after discontinuation. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia with a cross reference to section 4.8, where "infection" with the frequency "very common" was qualified to mention PJP. Section 4.8 also includes information that PJP was amongst the opportunistic infections observed in clinical studies, including after stopping idelalisib treatment and that most PJP cases, including fatal cases, occurred in patients that did not receive prophylaxis. The PRAC was also of the view that cases of PJP should be closely monitored; to this effect a targeted follow up questionnaire has been included in a revised RMP. The MAH should implement these questionnaires and their results should be discussed in future PSURs.

- ***Cytomegaloviral infection***

In relapsed/refractory CLL patients serious CMV infections occurred only in association with bendamustine, whilst small numbers of non-serious CMV cases were observed in all studies. CMV infections occurred predominantly in the treatment arms of studies evaluating idelalisib in combination with both rituximab and bendamustine. The majority of CMV cases (75% [39/52]) occurred within the first 6 month of treatment. Similarly as for PJP infection, while more cases occurred during the first 6 months of treatment considering the proportion of cases also occurring later, it was not considered appropriate to limit the CMV monitoring to this fixed period of time.

Overall, there was no clear relationship to treatment duration or number of prior regimen.

In the clinical studies, the risk of CMV appears particularly evident in patients administered idelalisib and rituximab in combination with bendamustine. While it is acknowledged that the frequency of CMV might have been underestimated as symptoms of CMV infection are relatively unspecific and no regular screening for CMV (e.g. polymerase chain reaction [PCR]) was performed in the studies, in patients treated with idelalisib in combination with rituximab or ofatumumab in controlled studies (GS-US-312-0116, GS-US-312-0119 and GS-US-313-0124), the event rate of CMV was low (1%). The SAG advised that monitoring was only needed in patients with positive serology at start of treatment with idelalisib. This was agreed by the PRAC, which added that patients with other evidence of a history of CMV infection should also be monitored. In addition, the SAG considered that patients with increased viraemia compared to baseline should be carefully monitored but that idelalisib treatment should be continued. If clinical signs of CMV infection occur in these patients, then consideration should be given to interrupting idelalisib until the infection has resolved, weighting the need for idelalisib treatment against the severity of the CMV symptoms. The PRAC considered these recommendations appropriate. The SAG further advised that if the benefits of resuming idelalisib are judged to outweigh the risk, consideration should be given to administering pre-emptive CMV therapy. The PRAC considered that CMV should be added to further qualify the nature of the serious infections listed as adverse reactions in section 4.8 of the SmPC and that it should be further described that these were amongst the opportunistic infections reported in the idelalisib arms of clinical studies. The MAH should closely monitor cases of CMV and discuss these in detail in future PSURs.

Conclusion

The results of study GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 are considered of limited relevance to the benefit-risk balance of idelalisib in the authorised indication and to the benefit-risk balance of idelalisib in combination with ofatumumab in CLL patients.

The PRAC concluded that the benefit-risk balance in the authorised indications remained positive, provided that first line treatment with idelalisib is only used in patients with 17p deletion or TP53 mutation that are not eligible for any other therapies and that changes are implemented in the product information to minimise the risk of serious infections. The PRAC considered that these measures should be applied for the use of idelalisib in combination with ofatumumab in CLL patients.

2.6.1. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 18/03/2016.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 1.7 (dated 22 January 2016) is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

Following the outcome of the Article 20 referral, the PRAC and CHMP also endorsed RMP version 1.18 (dated 20 July 2016), combining the RMP versions 1.17 and 1.7, approved within the Article 20 referral (positive CHMP opinion dated 21 July 2016) and variation EMEA/H/C/003843/II/0011, respectively, with the following contents.

Safety concerns

Table 57: Summary of safety concerns

Important Identified Risks	Transaminase elevation
	Severe diarrhoea/colitis
	Pneumonitis
	Neutropenia
	Rash
	Stevens-Johnson syndrome (SJS) – Toxic epidermal necrolysis (TEN)
	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 of patients with concomitant immunization
	Immunological effects and auto-immunity
	Safety in children
	Safety of breastfeeding
	Drug-drug interaction with oral contraceptive

Pharmacovigilance Plan

Table 58: Ongoing and planned studies in the PhV development plan

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 1 (Interventional studies)				
Study GS-US-312-0117 (A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia. [*A Companion Trial to Study GS-US-312-0116]*)	Evaluate the safety and efficacy of idelalisib plus rituximab in subjects with relapsed CLL	Long term safety and efficacy	Ongoing	Interim update submitted: October 2014 Second interim update submitted: 15 July 2015 Final CSR due for submission: Q4 2017
Study 101-09 (A Phase 2 Study to Assess the Efficacy and Safety of CAL-101 in Patients With Indolent B-Cell Non-Hodgkin Lymphoma Refractory to Rituximab and Alkylating Agents)	Evaluate the safety and efficacy of idelalisib monotherapy in subjects with refractory iNHL	Long term safety and efficacy	Ongoing	December 2016
Study 101-99 (An Extension Study to Investigate the Safety and Durability of Clinical Activity of CAL-101 in Patients With Hematologic Malignancies)	Evaluate the safety and efficacy of idelalisib monotherapy in subjects with refractory iNHL	Long term safety and efficacy	Ongoing	Interim update submitted: 09 December 2014 Final report due for submission: Q3 2017
Category 3 (Interventional studies)				
BP-US-313-0128 – Open-label, nonrandomised, multi-centre, multiple-dose trial to evaluate pharmacokinetics and tolerability of idelalisib in children from 1 to less than 18 years of age with a relapsed or refractory mature B-cell neoplasm	To evaluate the PK and tolerability of idelalisib in adolescents and children	Safety in children	Planned	Deferred

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
BP-US-313-0129 – Randomised, multi-centre, placebo-controlled trial to evaluate safety and efficacy of idelalisib in combination with on top of standard of care multi-agent anti tumour chemotherapy in children from 1 to less than 18 years of age with a relapsed or refractory mature B-cell neoplasm	To evaluate the safety and efficacy of idelalisib in adolescents and children	Safety in children	Planned	Deferred
Study 101-08 (A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of CAL-101 in Combination With Rituximab in Elderly Patients With Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma)	To evaluate safety and efficacy of idelalisib in combination with rituximab in untreated elderly subjects with CLL	Long term safety and data to further support efficacy in patients with 17p Deletion/ *TP53* Mutation	Study terminated	Q4 2017
Study 101-07 (A Phase I Study to Investigate the Safety and Clinical Activity of CAL 101 in Combination with Chemotherapeutic Agents and Anti CD20 mAb in Patients with Relapsed or Refractory Indolent B cell Non Hodgkin Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia)	Evaluate safety and efficacy of idelalisib in subjects with relapsed/refractory iNHL and CLL	Long term safety and data to further support efficacy in patients with 17p Deletion/ *TP53* Mutation	Study completed Final Study Report date 02 October 2015	Q3 2017
Study BP-US-312-1616 An in vivo interaction (induction) study with oral contraceptive	To evaluate the effect of idelalisib co-administration on the PK of a representative oral contraceptive	Drug-drug interaction with oral contraceptive	Planned	Feasibility report submitted 27 February 2015 Response to supplementary information submitted 30 July 2015; further RSI received 22 October 2015

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
European HCP Survey	To measure the effectiveness of the Direct Healthcare Professional Communication that notified prescribers of the risk of serious and/or fatal infections including opportunistic infections such as PJP and CMV in first line treatment of CLL and early line iNHL	*Important identified risk*: Serious and/or fatal infections including opportunistic infections such as PJP and CMV	Planned	Submission of survey protocol: Q4 2016 Survey data collection: End of Q1 2017 Final report: End of Q3 2017/ Early Q4 2017
Post-Authorisation Safety Study (PASS)/ registry	To further characterize the toxicity and safety profile of idelalisib in real life use in refractory FL patients	Safety of idelalisib in real life use in refractory FL patients	Planned	Submission of protocol: Within 3 months of EC decision Date of initiation: To be determined Final report: To be determined
Category 3 (Nonclinical studies)				
TX-312-2017 – A 2-Year Oral (Gavage) Carcinogenicity Study of Idelalisib in Sprague Dawley Rats	To evaluate carcinogenicity with idelalisib therapy	Carcinogenicity	Ongoing	Q2 2017
Study TX-312-2019 – 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Idelalisib in RasH2 [001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic] Mice	To evaluate carcinogenicity with idelalisib therapy	Carcinogenicity	Planned	Q2 2017
Drug mechanism of resistance studies for CLL (PC-312-2018, samples collected from completed and ongoing studies: GS-US-312-0116, GS-US-312-0117 and GS-US-312-0119) and iNHL	To investigate the mechanism of drug resistance with idelalisib	Development of of drug resistance	Ongoing	June 2016 (CLL) To be determined (iNHL)

Risk minimisation measures

Table 59: Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risk(s)		
Transaminase elevation	The SmPC section 4.2, Posology and method of administration, provides instruction for dose modification in the event of elevated liver transaminases: "Treatment with Zydelig must be withheld in the event of a Grade 3 or 4 aminotransferase elevation (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] > 5 x upper limit of normal [ULN]). Once values have returned to Grade 1 or below (ALT/AST ≤ 3 x ULN), treatment can be resumed at 100 mg twice daily. If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, treatment with Zydelig must be withheld until the values return to Grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician (see sections 4.4 and 4.8)." Section 4.4, Special warnings and precautions for use, states: "Elevations in ALT and AST of Grade 3 and 4 (> 5 x ULN) have been observed in clinical studies of idelalisib. These laboratory findings were generally observed within the first 12 weeks of treatment, were generally asymptomatic, and were reversible with dose interruption. Most patients resumed treatment at a lower dose without recurrence (see section 4.2). ALT, AST, and total bilirubin must be monitored in all patients every 2 weeks for the first 3 months of treatment, then as clinically indicated. If Grade 2 or higher elevations in ALT and/or AST are observed, patients must be monitored weekly until the values return to Grade 1 or below." Section 4.8, Undesirable effects, lists "transaminase increased" as a very common (≥ 10%) adverse drug reaction.	None

Severe diarrhoea/colitis	The SmPC section 4.2, Posology and method of administration, provides instruction for dose modification in the event of diarrhoea: “Treatment with Zydelig must be withheld in the event of Grade 3 or 4 diarrhoea/colitis. Once diarrhoea/colitis has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8).” Section 4.4, Special warnings and precautions for use, states: “Cases of severe drug-related colitis occurred relatively late (months) after the start of therapy sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment (e.g., anti-inflammatory agents such as enteric budesonide). There is very limited experience from the treatment of patients with a history of inflammatory bowel disease.” Section 4.8, Undesirable effects, lists “Diarrhoea/colitis” as a very common (≥ 10%) adverse drug reaction.	None
Pneumonitis	The SmPC, section 4.2, Posology and method of administration, states: “Treatment with Zydelig must be withheld in the event of suspected pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg twice daily can be considered (see sections 4.4 and 4.8).” The SmPC, section Section 4.4, Special warnings and precautions for use, states: “Cases of pneumonitis have been reported in clinical studies with idelalisib. Patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis. If pneumonitis is suspected, idelalisib should be interrupted and the patient treated accordingly. Treatment must be discontinued for moderate or severe symptomatic pneumonitis.” Section 4.8, Undesirable effects, lists “pneumonitis” as a common (≥ 1%) adverse drug reaction.	None

<table>
<tr>
<td>Neutropenia</td>
<td>The SmPC, section 4.2, Posology and method of administration, states: “Treatment with Zydelig should be withheld in patients while absolute neutrophil count (ANC) is below 500 per mm3. ANC should be monitored at least weekly until ANC is ≥ 500 per mm^3 when treatment can be resumed at 100 mg twice daily (see section 4.4).”
<table>
<tr><th>ANC 1,000 to < 1,500/mm^3</th><th>ANC 500 to < 1,000/mm^3</th><th>ANC < 500/mm^3</th></tr>
<tr><td>Maintain Zydelig dosing.</td><td>Maintain Zydelig dosing.

Monitor ANC at least weekly.</td><td>Interrupt Zydelig dosing.

Monitor ANC at least weekly until ANC ≥ 500/mm^3, then may resume Zydelig dosing at 100 mg twice daily.</td></tr>
</table>
The SmPC, section 4.4, Special warnings and precautions for use, states:

“Neutropenia

Treatment-emergent Grade 3 or 4 neutropenia, including febrile neutropenia, have occurred in patients treated with idelalisib. Blood counts should be monitored in all patients at least every 2 weeks for the first 6 months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm^3 (see section 4.2).”

The SmPC Section 4.8, Undesirable effects, lists “neutropenia” as a very common (≥ 10%) adverse drug reaction.</td>
<td>Direct Healthcare Professional Communication</td>
</tr>
</table>

Rash	The SmPC Section 4.2, Posology and method of administration states: "Treatment with Zydelig must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If rash does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8)." Section 4.8, Undesirable effects, lists "rash" as a very common (≥ 10%) adverse drug reaction (Any Grade) and common (≥ 1 to <10%) for Grade ≥ 3. Section 4.8, Undesirable effects, Description of selected adverse reactions states: "Rash was generally mild to moderate and resulted in discontinuation of treatment in 1.7% of subjects. In studies 312-0116/0117 and 312-0119, rash (reported as dermatitis exfoliative, rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, and skin disorder) occurred in 28.3% of subjects who received idelalisib + an anti-CD20 monoclonal antibody and 7.7% who received an anti-CD20 monoclonal antibody only. Of these, 4.9% who received idelalisib + an anti-CD20 monoclonal antibody and 1.0% who received an anti-CD20 monoclonal antibody only had rash of Grade 3, and no subjects had an adverse event of Grade 4. Rash typically resolved with treatment (e.g., topical and/or oral steroids, diphenhydramine) and dose interruption for severe cases (see section 5.3, phototoxicity)."	None
SJS-TEN	Text in SmPC: Section 4.4, Special warnings and precautions for use: "Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with fatal outcomes have been reported when idelalisib was administered concomitantly with other medicinal products associated with these syndromes. If SJS or TEN is suspected, idelalisib should be immediately interrupted and the patient treated accordingly." Section 4.8, Undesirable effects, Description of selected adverse reactions: "Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4) Rarely, cases of SJS and TEN have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (bendamustine, rituximab, allopurinol, and amoxicillin). SJS or TEN occurred within one month of the medicinal combination and fatal outcomes have resulted."	None

Serious infections including opportunistic infections such as PJP and CMV	The SmPC, section 4.4, special warnings and precautions for use, states: "Serious infections Treatment with Zydelig should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection.Serious and fatal infections have occurred with idelalisib, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV). Prophylaxis for PJP should therefore be administered to all patients throughout idelalisib treatment, and for a period of 2 to 6 months after discontinuation. The duration of post-treatment prophylaxis should be based on clinical judgment and may take into account a patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia (see section 4.8). Patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new respiratory symptoms promptly.Regular clinical and laboratory monitoring for CMV infection is recommended in patients with positive CMV serology at the start of treatment with idelalisib or with other evidence of a history of CMV infection. Patients with CMV viraemia without associated clinical signs of CMV infection should be carefully monitored. For patients with evidence of CMV viraemia and clinical signs of CMV infection, consideration should be given to interrupting idelalisib until the infection has resolved. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy." Section 4.8, Undesirable effects, lists "infections (including *Pneumocystis jirovecii* pneumonia and CMV)" as a very common (≥ 10%) adverse drug reaction, and states under "Description of selected adverse reactions": "Higher frequencies of infections overall, including Grade 3 and 4 infections, were observed in the idelalisib arms compared to the control arms of idelalisib clinical studies. Most frequently observed were infections in the respiratory system and septic events. In many instances the pathogen was not identified; however, both conventional and opportunistic pathogens, including PJP and CMV, were among those identified. Nearly all PJP infections, including fatal cases, occurred in the absence of PJP prophylaxis. There have been cases of PJP after stopping idelalisib treatment."	Direct Healthcare Professional Communication
Off label use (first line CLL or early line iNHL)	The SmPC, section 4.1 Therapeutic indications, states: Zydelig is indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy (see section 4.4), or • as first line treatment in the presence of 17p deletion or *TP53* mutation in patients who are not eligible for any other therapies (see section 4.4).	Direct Healthcare Professional Communication
Important potential risk(s)		
Reproductive toxicity including teratogenicity	The SmPC Section 4.4, Special warnings and precautions for use states: "Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1-month after stopping treatment (see section 4.6). Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives." The SmPC Section 4.6, Fertility, pregnancy and lactation	None

	states: "Women of childbearing potential: Based on findings in animals, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking Zydelig, and for up to 1 month after ending treatment. Therefore, women of reproductive potential must use highly effective contraception while taking Zydelig and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception.	
	Pregnancy: There are no or limited amount of data from the use of idelalisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Zydelig is not recommended during pregnancy and in women of childbearing potential not using contraception. Fertility: No human data on the effect of idelalisib on fertility are available. Animal studies indicate the potential for harmful effects of idelalisib on fertility and foetal development (see section 5.3)." Section 5.3, Preclinical safety data states under "Reproductive and Developmental Toxicity": "In an embryo-foetal development study in rats, increased post-implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations and lower foetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC. Effects on embryo-foetal development were not investigated in a second species. Degeneration of the seminiferous tubules in the testes was observed in 2- to 13-week repeated dose studies in dogs and rats, but not in studies of 26 weeks and longer duration. In a rat male fertility study, decreases in epididymides and testes weight were observed but no adverse effects on mating or fertility parameters, and no degeneration or loss in spermatogenesis were observed. Female fertility was not affected in rats."	None
Drug-drug interaction with CYP3A inducers	The SmPC, section 4.4, Special warnings and precautions for use states "CYP3A inducers: Idelalisib exposure may be reduced when co-administered with CYP3A inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine. Since a reduction in idelalisib plasma concentrations may result in decreased efficacy, co-administration of Zydelig with moderate or strong CYP3A inducers should be avoided (see section 4.5)." The SmPC, section 4.5, Interaction with other medicinal products and other forms of interaction, recommend to avoid co-administration of idelalisib with strong CYP3A inducers: "*CYP3A Inducers*: A clinical drug interaction study found that co-administration of a single dose of 150 mg idelalisib with rifampicin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib AUC_{inf}. Co-administration of Zydelig with moderate or strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine should be avoided as this may result in decreased efficacy (see section 4.4)."	None
Drug-drug interaction with CYP3A substrates	The SmPC, section 4.4, Special warnings and precautions for use, states "The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. Thus, idelalisib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product (see section 4.5). When idelalisib is co-administered with other medicinal products, the Summary of Product	None

	Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening side effects (eg., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible." The SmPC, section 4.5, Interaction with other medicinal products and other forms of interaction, recommend caution if Zydelig is co-administered with CYP3A substrates: "*CYP3A Substrates:* The primary metabolite of idelalisib, GS-563117, is a strong CYP3A inhibitor. A clinical drug interaction study found that co-administration of idelalisib with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C_{max} and a ~440% increase in AUC_{inf} of midazolam due to the CYP3A inhibition by GS-563117. Co-administration of idelalisib with CYP3A substrates may increase their systemic exposures and increase or prolong their therapeutic activity and adverse reactions. *In vitro*, the CYP3A4 inhibition was irreversible, and return to normal enzyme activity is therefore expected to take several days after stopping idelalisib administration. Potential interactions between idelalisib and co-administered medicinal products that are CYP3A substrates are listed in Table 1 (increase is indicated as "↑"). This list is not exhaustive and is intended to serve as guidance only. In general, the SmPC for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors (see section 4.4)."	
Photosensitivity	The SmPC section 5.3, Preclinical safety data states "Evaluation of the potential for phototoxicity in the embryonic murine fibroblast cell line BALB/c 3T3 was inconclusive for idelalisib due to cytotoxicity in the in vitro assay. The major metabolite, GS-563117, may enhance phototoxicity when cells are simultaneously exposed to UVA light. There is a potential risk that idelalisib, via its major metabolite, GS-563117, may cause photosensitivity in treated patients. "	None
Skin cancer	Update of labeling based on analysis of data that may arise from any ongoing or future studies.	None
Missing Information		
Development of drug resistance	Update of labeling based on analysis of data that may arise from any ongoing or future studies.	None
Carcinogenicity	Update of labeling based on analysis of data that may arise from any ongoing or future studies.	None
Long-term safety	Update of labeling based on analysis of safety data that may arise from any ongoing or future studies.	None
Safety in patients with severe hepatic impairment	The SmPC sections 4.2, states: "No dose adjustment is required when initiating treatment with Zydelig in patients with mild or moderate hepatic impairment, but an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2). There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Therefore, caution is recommended when administering Zydelig in this population and an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2)."	None
	The SmPC, section 4.4, states: "Intensified monitoring of adverse reactions is recommended	

	in patients with impaired hepatic function as exposure is expected to be increased in this population, in particular in patients with severe hepatic impairment. No patients with severe hepatic impairment were included in clinical studies of idelalisib. Caution is recommended when administering Zydelig in this population." The SmPC, section 5.2, states: "A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, idelalisib AUC total, (i.e., bound plus unbound) was ~60% higher in moderate and severe impairment compared to matched controls. The idelalisib AUC (unbound), after accounting for differences in protein binding, was ~80% (1.8-fold) higher in moderate and ~152% (2.5-fold) higher in severe impairment compared to matched controls."	
Safety in patients with severe renal impairment	The SmPC sections 4.2, states: "No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 5.2)." The SmPC section 5.2, states: "A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with severe renal impairment (estimated CrCl 15 to 29 mL/min). Following a single 150 mg dose, no clinically relevant changes in exposures to idelalisib or GS-563117 were observed in subjects with severe renal impairment compared to healthy subjects."	None
Safety in patients with chronic active hepatitis	The SmPC, section 4.4, states under Special warnings and precautions for use: "Chronic hepatitis: Idelalisib has not been studied in patients with chronic active hepatitis including viral hepatitis. Caution should be exercised when administering Zydelig in patients with active hepatitis."	None
Safety of patients with concomitant immunisation	Update of labeling based on analysis of data that may arise from any ongoing or future studies.	None
Immunological effects and auto-immunity	Update of labeling based on analysis of data that may arise from any ongoing or future studies.	None
Safety in children	The SmPC, section 4.2, states under paediatrics: "The safety and efficacy of Zydelig in children under the age of 18 years have not been established. No data are available."	None
Safety of breastfeeding	The SmPC, section 4.6, states under fertility, pregnancy and lactation: "It is not known whether idelalisib and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Zydelig."	None
Drug-drug interaction with oral contraceptive	The SmPC section 4.4, Special warnings and precautions for use states: "Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1-month after stopping treatment (see section 4.6). Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives."	None

	The SmPC section 4.6, Fertility, pregnancy and lactation states: "Based on findings in animals, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking Zydelig, and for up to 1 month after ending treatment. Therefore, Women of childbearing potential must use highly effective contraception while taking Zydelig and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception."	

The applicant is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

– No user consultation with target patient groups on the package leaflet has been performed on the basis that the change to the leaflet is only a very minor alteration wording to reflect a new combination of idelalisib with ofatumumab.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The analysis of the primary endpoint PFS was based on the ITT Analysis Set and stratified by 17p deletion and/or TP53 mutation, IGHV mutation, and disease status. With an overall event rate of ~50%, a total of 43.7% of the idelalisib + ofatumumab group and 62.1% of the ofatumumab alone group experienced a PFS event according to the IRC, with an adjusted HR (95% CI) of 0.27 (0.19, 0.39) and 2-sided p-value of < 0.0001 based on a stratified log-rank test. The median PFS (95% CI) was 16.3 (13.6, 17.8) months for subjects in the idelalisib + ofatumumab group and 8.0 (5.7, 8.2) months for subjects in the ofatumumab alone group.

Based on the IRC assessment (ITT Analysis Set), the ORR (classified as CR or PR) (95% CI) was 75.3% (68.2%, 81.5%) for the idelalisib + ofatumumab group and 18.4% (10.9%, 28.1%) for the ofatumumab alone group. The odds ratio favored idelalisib + ofatumumab compared with ofatumumab alone (p < 0.0001).

The results from the primary and secondary efficacy endpoints were consistent in all subpopulations analysed including those of subjects with or without 17p deletion and/or TP53 mutation. This is also consistent with the findings observed in study GS-US-312-0116 study using rituximab as combination therapy.

Uncertainty in the knowledge about the beneficial effects

There is uncertainty concerning the magnitude of the effect on OS for the combination of idelalisib and ofatumumab in the long term. For study GS-US-312-0116, a highly statistically significant HR = 0.34 (95%CI 0.19, 0.60, p-value=0.0001) in favour of the idelalisib+rituximab arm was achieved. A similar OS was expected for study GS-US-312-0119, however, the HR=0.74 was not statistically significant (95%CI 0.44, 1.24; p-value=0.27). Confounding factors such as a imbalanced high discontinuation rate in the control ofatumumab arm of patients without an event, the open label design of the study and the results of the study GS-US-312-0116 becoming publically available, which may have led to patients changing to other effective therapies in the course of their treatment, could have accounted for the lack of benefit in OS and of the difference observed between the two studies. Although an effect on OS has not been observed, a detrimental effect is not expected. The favourable efficacy demonstrated in terms of the convincing PFS and the positive trend observed in OS supports the overall clinical benefit in the combination treatment with ofatumumab in the CLL patient population.

Combination of idelalisib with anti-CD20 MAbs other than rituximab or ofatumumab has not been reported. Considering the different mechanism of action of type I and type II CD20 MAbs, further data would be needed to support combination with type II anti-CD20 MAbs. Therefore, the combination with ofatumumab has been specifically stated in the indication as there is not enough data to support a broad indication with any anti-CD20 antibodies.

Risks

Unfavourable effects

Adverse events related to idelalisib were reported for ~90% of subjects, and in 67% of these AEs were grade ≥3. In comparison, AEs related to ofatumumab was reported in 79% (grade ≥3 in 47%) and 78% (grade ≥3 in 34%) in the idelalisib + ofatumumab arm and ofatumumab arm, respectively.

Serious AEs were reported for 69.9% of the idelalisib + ofatumumab group and 41.9% of the ofatumumab alone group. Adjusting for exposure time, the incidence rate (95% CI) for SAEs was 1.14 per year in the ofatumumab + idelalisib arm and 1.40 per year in the ofatumumab arm. The most frequently reported SAEs in the idelalisib + ofatumumab arm were pneumonia and febrile neutropenia (each 11.6%), pyrexia (11.0%), and diarrhoea (9.8%). In the ofatumumab arm, the most frequent SAEs were pneumonia (10.5%) and febrile neutropenia (3.5%). All other SAEs occurred in 2 or fewer subjects.

As expected from the safety profile of idelalisib, the incidence of AEs for the identified risks of transaminase elevations, severe diarrhoea/colitis, pneumonitis, neutropenia, and rash, were more frequently seen in the idelalisib + ofatumumab arm.

Pneumonia of any grade was reported in 24.9% (18% ≥Grade 3) of the idelalisib + ofatumumab arm, and in the ofatumumab arm, 17.4% had pneumonia of any grade (10.5% ≥Grade 3). Seven subjects in the idelalisib + ofatumumab group discontinued study drug due to pneumonia.

AEs leading to dose interruption, dose reduction, and study drug discontinuation were more frequent in the idelalisib + ofatumumab arm (see SmPC section 4.2).

Tolerability of the combined regimen of idelalisib and ofatumumab appeared to be worse than for study GS-US-312-0116 since discontinuation of idelalisib in the combination arm with ofatumumab was 30.6% compared to 17.3% in study GS-US-312-0116 with rituximab combination treatment. Taking into account the caveat that comparisons between the trials are made more difficult due to different length of follow-up, the incidences of AEs seem overall consistent with what is already known from both studies and no unexpected safety concerns to patients is expected.

Uncertainty in the knowledge about the unfavourable effects

There are important potential risks that have been identified in the initial marketing application: reproductive toxicity including teratogenicity, drug-drug interaction with CYP3A inducers, drug-drug interaction with CYP3A substrates, photosensitivity and skin cancer. These are currently managed through recommendations in the SmPC, routine risk minimization activities in the RMP and routine pharmacovigilance.
There is uncertainty over the missing information concerning the 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 of patients with concomitant immunization, immunological effects and auto-immunity, safety in children, safety of breastfeeding and drug-drug interaction with oral contraceptive. These safety concerns are being managed through recommendations in the SmPC, routine risk minimization activities in the RMP and routine pharmacovigilance. No new safety concerns have been identified with the combination of idelalisib+ofatumumab combination.

Effects Table

Table 60: Effects Table for idelalisib + ofatumumab vs ofatumumab [control] (data cut-off: 15-JAN-2015)

Effect	Short Description	Unit	idelalisib + ofatumumab	ofatumumab	Uncertainties/ Strength of evidence	Comment
Favourable Effects						
PFS	Median KM estimate (95% CI)	months	16.3 (13.6, 17.8)	8.0 (5.7, 8.2)	Adj HR 0.27 P<0.0001	Event rate overall ~50% (44% I+O vs. 62% O)
ORR	CR + PR/N	%	75.3	18.4	OR 15.94 P<0.0001	Convincing
LNR rate	% subjects achieving ⩾50% decrease from baseline	%	93.3	4.9	OR 486.96 P<0.0001	Convincing
OS	Median KM estimate (95% CI)	months	20.9 (20.9, NR)	19.4 (16.9, NR)	Adjusted HR (95% CI) 0.74 (0.44, 1.25) P=0.27	Event rate ~25% in each arm
PFS in subgroup with 17p deletion and/or TP53 Mutation	Median KM estimate (95% CI)	months	13.7 (11, 17.8)	5.8 (4.5, 8.4)	Unadjusted HR (95% CI) 0.32 (0.18, 0.57)	Event rate overall ~53% (50% I+O vs. 61% O)
Unfavourable Effects						

Effect	Short Description	Unit	idelalisib + ofatumumab	ofatumumab	Uncertainties/ Strength of evidence	Comment
Total AEs		%	99.4	98.8		
Total AEs grade≥3		%	87.9	55.8		
Diarrhoea /colitis grade≥3		%	≥48 20.2	≥23.3 1.2		
Pneumonia grade≥3		%	24.9 17.9	17.4 10.5		
Pneumonitis grade≥3		%	6.4 4.6	0		
Rash grade≥3		%	28.3 4.0	10.5 2.3		
Discontinued idelalisib due to AE		%	30.6	NA		
Discontinued ofatumumab due to AE			9.2	23.3		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The clinical benefit of idelalisib in combination with ofatumumab has been demonstrated with a prolongation in PFS of approximately 8 months. This result is statistically significant and clinically relevant in this patient population. Differences between the arms in ORR and lymph node response rate are also substantial and clearly indicate higher efficacy when ofatumumab (in a dose reduced by 50%) is combined with idelalisib. Furthermore, the higher efficacy of idelalisib + ofatumumab in these respects seems consistent in all subgroups including notably patients with high-risk prognostic features such as del 17p/TP53-mutations and those with unmutated IgHV-chains. No statistically significant effect was associated to idelalisib+ofatumumab compared to ofatumumab in terms of overall survival although a detrimental effect seems unlikely. The safety data did not raise any specific concerns.

Benefit-risk balance

The CHMP considers that the benefits of idelalisib + ofatumumab in terms of PFS in patients with CLL outweigh the risks. Therefore, the CHMP considers that the benefit risk balance is positive.

Discussion on the Benefit-Risk Balance

With the emergence of new therapies, prolonged disease control and survival has been achieved in patients with advanced CLL including those with high-risk prognostic factors such as del17p/TP53-mutations. However, complete remissions are still rare which presumably requires continuation of therapy. This increases the importance of optimizing treatment also from a tolerability perspective.

The benefit of the combination of idelalisib+ofatumumab has been demonstrated in the pivotal study GS-US-312-0119 in terms of PFS with a difference of 8.3 months compared to the ofatumumab treatment arm. This compares, although somewhat lower, with the PFS demonstrated in the GS-US-312-0116 study with the combination of rituximab+idelalisib of 12.9 months. Surprisingly, a statistically significant difference in OS was not observed with idelalisib+ofatumumab, compared with ofatumumab (HR: 074; 95%CI 0.44, 1.25; p-value 0.27). This is in contrast with the results obtained in study GS-US-312-0116 where there was a clear OS advantage observed in the rituximab combination arm (HR:0.34; 95%CI 0.19,0.60; p-value= 0.0001). It is possible that disproportional early discontinuation without events, perhaps as a result of informative censoring due to the open label design and early results from GS-US-312-0116 study, may have confounded the OS results. However, a mechanistic explanation could also be plausible. Although ofatumumab and rituximab both target CD20, the binding epitopes are different as well as their patterns of cytotoxic effects. Rituximab and ofatumumab have not been directly compared in clinical studies in CLL and their relative efficacy and tolerability/toxicity have not been assessed. It is acknowledged that indirect comparisons between studies are complicated by different study designs and length of follow-up in the various studies.

The smaller effect size in study GS-US-312-0119 should also be weighed against the safety findings. Tolerability of the combined regimen of idelalisib and ofatumumab appeared to be worse than for study GS-US-312-0116 since discontinuation of idelalisib in the combination arm with ofatumumab was 30.6% compared to 17.3% in study GS-US-312-0116 with rituximab combination treatment. Again, different lengths of follow-up confound the indirect comparisons from the study findings. The safety and tolerability of the combination therapy appears to be acceptable and manageable through SmPC recommendations, routine pharmacovigilance and implementation of RMP measures.

Further to the assessment of emerging safety information under Article 20 of Regulation (EC) reviewed data on the interim results of studies GS-US-312-0123, GS-US-313-0124, GS-US-313-0125 that suggested an increased risk of death and serious infection with idelalisib were reviewed. The results of these studies were considered of limited relevance for the benefit-risk balance of idelalisib in its authorised indications and ongoing extension of indication in combination with ofatumumab for the treatment of CLL. Nevertheless, as a precaution and in view of the fact that limited data are available in treatment-naïve CLL patients with 17p deletion or *TP53* mutation, the PRAC recommended that idelalisib should only be used in this group of patients if they are not eligible for any other therapies. Further minimisation measures of the known risk of infection related to the use of idelalisib and changes to the product information were agreed.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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

Extension of Indication for Zydelig to include the combination of idelalisib with ofatumumab; 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 for United Kingdom, Ireland, Slovenia and Slovakia in the Package Leaflet. Furthermore, as a consequence of the art 20 referral procedure (EMEA/H/A-20/1439/C/003843/0023) sections 4.1, 4.4, 4.8 of the SmPC and the package leaflet are updated with a further change introduced in the indication so that idelalisib can be used as first line in patients with 17p deletion or TP53 mutation if they are not eligible for any other therapies.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zydelig is not similar to Imbruvica, Gazyvaro and Arzerra within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication for Zydelig to include the combination of idelalisib with ofatumumab; 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 for United Kingdom, Ireland, Slovenia and Slovakia in the Package Leaflet. Furthermore, as a consequence of the art 20 referral procedure (EMEA/H/A-20/1439/C/003843/0023) sections 4.1, 4.4, 4.8 of the SmPC and the package leaflet are updated with a further change introduced in the indication so that idelalisib can be used as first line in patients with 17p deletion or TP53 mutation if they are not eligible for any other therapies.

Summary

Please refer to the published assessment report Zydelig-H-C-3843-II-0011-AR.