27 June 2019
EMA/CHMP/644926/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imbruvica

International non-proprietary name: ibrutinib

Procedure No. EMEA/H/C/003791/II/0046

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AV	Atrioventricular
BR	Bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CIT	Chemoimmunotherapy
CLL	Chronic lymphocytic leukemia
CrCl	Creatinine clearance
CRR	Clinical response rate
CTCAE	Common Terminology Criteria for Adverse Events
del17p	Deletion of chromosome 17p
DILI	Drug-induced liver injury
DOR	Duration of response
ECOG	European Cooperative Group
EMA	European Medicines Agency
EU	European Union
GI	Gastrointestinal
HR	Hazard ratio
Ig	Immunoglobulin
ILD	Interstitial lung disease
IPSS	International Prognostic Scoring System
IRC	Independent Review Committee
IRRs	Infusion-related reactions
ISS	Integrated Summary of Safety
IV	Intravenous
IWWM	International Workshops on WM
LPL	Lymphoplasmacytic lymphoma
LTS	Long term safety
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor response
MRU	Medical resource utilisation
NCI	National Cancer Institute
NE	Not estimable
NF-kB	Nuclear factor kappa light chain enhancer of activated B cells
NMSC	Non-melanoma skin cancer
OS	Overall survival
PBRER	Periodic Benefit Risk Evaluation Report
PFS	Progression free survival
PML	Progressive multifocal leukoencephalopathy
PMR	Postmarketing requirement
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RR	Response rate
RMP	Risk Management Plan
ROW	Rest of world
SCAR	Severe cutaneous adverse reactions
SCS	Summary of Clinical Safety
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
WM	Waldenström's macroglobulinemia

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 12 November 2018 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 to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab; as a consequence, section 4.1 and 4.8 of the SmPC is updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) was submitted.

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

Imbruvica, was designated as an orphan medicinal product EU/3/14/1264 on 29 April 2014. Imbruvica was designated as an orphan medicinal product in the following indication: "Treatment of lymphoplasmacytic lymphoma".

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0271/2014 (for capsules) and P/0297/2017 (for film-coated tablets) on the granting of product-specific waivers.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 18 September 2013 (EMEA/H/SAH/022/1/2013/II). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

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Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	12 November 2018
Start of procedure:	1 December 2018
CHMP Rapporteur Assessment Report	28 January 2019
PRAC Rapporteur Assessment Report	1 February 2019
Updated PRAC Rapporteur Assessment Report	6 February 2019
PRAC Outcome	14 February 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 February 2019
Request for supplementary information (RSI)	28 February 2019
PRAC Rapporteur Assessment Report	03 June 2019
CHMP Rapporteur Assessment Report	12 June 2019
PRAC Outcome	13 June 2019
Updated CHMP Rapporteur Assessment Report	20 June 2019
Opinion	27 June 2019

2. Scientific discussion

2.1. Introduction

Ibrutinib (Imbruvica, PCI-32765) is a first-in-class, potent, orally-administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK).

The European Commission has approved ibrutinib in the EU for the following clinical situations:

- IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory MCL.
- IMBRUVICA as a single agent is indicated for the treatment of adult patients with previously untreated CLL.
- IMBRUVICA as a single agent or in combination with bendamustine and rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
- IMBRUVICA as a single agent is indicated for the treatment of adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo immunotherapy.

The current Type II variation concerns an extension of indication of the approval of ibrutinib in combination of rituximab for the treatment of patients with Waldenström macroglobulinemia (WM), regardless of line of therapy. Proposed addition to the existing indication statement for WM is shown below in italic text:

"IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo immunotherapy. *IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM".*

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Background on the Target Indication/Current Treatment

Waldenström macroglobulinemia (WM) is a distinct lymphoproliferative B-cell disorder characterized by infiltration of lymphoplasmacytic cells into the bone marrow along with demonstration of an immunoglobulin (Ig) M monoclonal gammopathy in the serum. It is a subtype of lymphoplasmacytic lymphoma (LPL) as defined by the Revised European-American Lymphoma and the World Health Organization (WHO) classification systems. The majority of LPL are WM. The definition WM exclude presentations of LPL associated with IgA or IgG gammopathies.

WM, which constitutes 1–2% of hematologic malignancies, is an orphan indication; the overall incidence in EU is estimated to be 7.3 and 4.2 per million among males and females, respectively and is a disease of the elderly, with incidence increasing with age, and median age being over 70 years. The most recognized risk factor for developing WM is IgM monoclonal gammopathy of undermined significance (MGUS), which confers a 46-fold higher relative risk compared to the general population.

Clinical manifestations of WM include cytopenias resulting from bone marrow infiltration by lymphoplasmacytic cells and IgM paraprotein related symptoms such as cryoglobulinemia, cold agglutinin syndrome, demyelinating neuropathy, and symptomatic hyperviscosity. In more rare cases, symptoms are derived from lymphadenopathy and splenomegaly/organomegaly.

WM remains an incurable disease with variability in outcome. Approximately 75% of patients are symptomatic and therefore require treatment to control symptoms related to tumor burden. Asymptomatic patients should be observed and serum IgM levels alone are not a basis for treatment.

Factors associated with a poor prognosis include advanced age (>65 years); β2-microglobulin >3 mg/L; anemia (hemoglobin ≤11.5 g/dL); thrombocytopenia (platelet count ≤100 x 10^9/L); and IgM monoclonal gammopathy (IgM >7.0 g/dL). Based on these key factors an international prognostic scoring system for newly diagnosed patients with WM was developed (WM IPSS score), indicating that the 5-year survival rates range from 36% to 87% in high- and low-risk patients, respectively.

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Table 1: Waldenström Macroglobulinemia International Prognostic Scoring System

WM IPSS Calculation

Factors associated with Prognosis	Value
Age	> 65 years
Hemoglobin	≤ 11.5 g/dL
Platelet count	≤ 100 x 10^9/L
β2-microglobulin	> 3 mg/L
Serum monoclonal IgM	> 7.0 g/dL
Risk Category	**Score**
I (low risk)	0 or 1 factors (≤ 65 years)
II (intermediate risk)	2 factors OR age > 65 years
III (high risk)	> 2 factors

An international prognostic scoring system for newly diagnosed WM patients was recently developed (Morel et al, 2009) based on 5 factors associated with a poor prognosis include advanced age, high beta 2-microglobulin ($ß_2M$), low albumin, cytopenias, serum IgM monoclonal protein, and organomegaly

	Low-risk	Intermediate-risk	High-risk
Number of risk factors	≤1 (excluding age)	2 or age >65 years	>2 risk factors
Percentage of patients	27%	38%	35%
5-year survival rate	87%	68%	36%
Reference: Morel 2009			

Rationale for Use of Ibrutinib in WM

Given the rarity of WM, most of the current treatment regimens have been adopted fron data derived fron phase 2 studies and less often from prospective trials addressed to WM as well as to other indolent B-cells lymphomas.

The rationale for the use of ibrutinib in this study was based on the results from a Phase 1 dose-escalation study (PCYC-04753), and an investigator-sponsored Phase 2 study (PCYC-1118E (NCT01614821) hereafter named study 1118E) that demonstrated single-agent activity in subjects with previously treated WM.

Recently, a somatic mutation of the MYD88 gene (L265P), was identified that appears to drive WM growth and proliferation. This mutation conveys tonic MYD88-interleukin 1 receptor associated kinase 1 (IRAK) signalling that activates BTK and the nuclear factor kappa light chain enhancer of activated B cells (NF-kB)/mitogen-activated protein kinase (MAPK) pathways, which are important for the growth and survival of WM cells.

Ibrutinib blocks MYD88 signalling downstream of BTK and leads to apoptosis of WM cell lines. Thus, ibrutinib specifically targets the molecular pathogenetic mechanism of WM. The prospective, Phase 2 single arm study of ibrutinib in previously treated patients with WM, study 1118E, demonstrated clinical benefit and a favorable safety profile, which 2015 lead to approval of ibrutinib in patients with WM.

Ibrutinib is, presently, the only therapeutic agent centrally approved for the treatment of WM in the EU, both in previously treated patients and as first-line treatment in patients for whom chemo-immunotherapy is unsuitable.

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Rituximab is not approved by in the EU for the treatment of WM, nonetheless it is the most commonly utilized agent in clinical practice, mostly in combination with chemotherapy and is recommended in European and US treatment guidelines to treat patients with treatment-naïve and previously treated WM. Monotherapy rituximab is known to exert its effect with low toxicity profile, lack of impact on the mobilization of peripheral blood stem cells, non-myelosuppressive treatment profile, and response rates either as a single agent (range: 20% to 45%) or in combination regimens (70% to 90%). Rituximab monotherapy is well tolerated although transient increases in serum IgM levels (IgM flare) have been reported in approximately 50% of patients and the most common adverse events were infusion-related reactions. An extended rituximab regimen (rituximab for 4 weeks and for those without progression at week 12, 4 additional weekly infusions of rituximab) reported higher response rates (44% and 48%).

Chemo immunotherapy (CIT) is a potent therapeutic option for WM due to the additive clinical effect of rituximab with purine analogues, alkylating agents, or proteasome inhibitors However, these combination therapies are often associated with more short- and long-term toxicity, including high rates of myelosuppression and myelodysplasia, in a population already vulnerable from the symptoms associated with the underlying disease.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No new data for the environmental risk assessment were provided with this application. A complete ERA has been provided in previous procedures, and considered acceptable. For this application, the MAH has provided an updated market forecast for calculation of PEC/PNEC ratios. These ratios remain far below 1.

2.2.2. Discussion and conclusion on non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable. From the ERA update the conclusion remains: The clinical use of ibrutinib is not expected to be a risk for the environment as there will be no significant increase in environmental exposure further to the use of imbruitinib.

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.

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- Tabular overview of clinical studies

Table 2 Description of Study PCYC-1127-CA

Study	Randomized Study Design	Randomized Study Population	Efficacy Evaluation	Number of Subjects	Median Time on Study (overall)
PCYC-1127-CA	Phase 3, randomized, placebo-controlled, multicenter, double-blind study evaluating the efficacy and safety of 420 mg ibrutinib plus 375 mg/m^2 rituximab vs. 375 mg/m^2 rituximab alone	Adult subjects (≥18 years of age) with a centrally confirmed clinicopathological diagnosis of WM with a measurable serum IgM >0.5 g/dL and symptomatic disease meeting at least 1 of the recommendations from the Second International Workshop on WM (Kyle 2003) and an ECOG performance status score of ≤2.	Primary: IRC assessed PFS Key Secondary: IRC assessed response rate (PR or better), TTnT, rate of sustained Hgb improvement, proportion of subjects with ≥3 points increase from baseline by Week 25 in FACIT-Fatigue subscale score, and OS	Randomized: 150 (75 ibrutinib+R vs. 75 placebo+R) Treated: 150 (75 ibrutinib+R vs. 75 placebo+R)	26.5 months
	Open-Label Substudy	**Open-Label Substudy Population**	**Efficacy Evaluations**	**Number of Subjects**	**Median Time on Study (overall)**
	Phase 3, open-label substudy evaluating the efficacy and safety of 420 mg ibrutinib as a monotherapy in subjects with WM who were refractory to the last prior rituximab-containing therapy.	Subjects meeting the eligibility criteria of the randomized study, who had WM that was refractory to the last prior rituximab-containing therapy.	Primary: IRC assessed PFS Key Secondary: IRC assessed response rate (PR or better), TTnT, rate of sustained Hgb improvement, proportion of subjects with ≥3 points increase from baseline by Week 25 in FACIT-Fatigue subscale score. and OS	Enrolled: 31 Treated: 31	34.4 months

ECOG=Eastern Cooperative Oncology Group; FACIT=Functional Assessment of Chronic Illness Therapy; IRC= independent review committee; Hgb=hemoglobin; OS=overall survival; PFS=progression-free survival; PR=partial response; R=rituximab; TTnT=time-to-next treatment; WM=Waldenström's macroglobulinemia

2.3.2. Pharmacokinetics

Methods

Study drug administration

In the study, treatment Arm A was administered ibrutinib (3 x 140 mg oral capsules) 420 mg/day and Rituximab (intravenous administration) 375 mg/m2 weekly for 4 consecutive weeks followed by a second four-weekly rituximab course after a three-month interval. Treatment Arm B was administered Placebo (3 capsules/day) and Rituximab 375mg/m2 IV weekly for 4 consecutive weeks followed by a second four-weekly rituximab course after a three-month interval.

In the open-label sub-study (Arm C) ibrutinib 420 mg/day was administered until disease progression or unacceptable toxicity.

Subjects were instructed to take the capsules at approximately the same time each day with 8 ounces (approximately 240 mL) of water. On day of Week 4, Day 22 PK visit (Arm A/B), ibrutinib/placebo was administered 0-30 minutes before rituximab infusion.

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Bioanalytical methods

The bioanalytical method (BTM-1792-R0) used for the measurement of ibrutinib and its metabolite PCI-452227 in study 1127 was previously assessed in application EMEA/H/C/3791/X/37. Blood samples (approximately 2 mL) were collected into Vacutainer® tubes containing sodium heparin from all subjects pre-dose. Plasma samples were stored at Frontage Laboratories at a nominal temperature of -70°C. Samples were analysed by a sensitive and specific LC-MS/MS method for the determination of ibrutinib and PCI-45227 in heparinized human plasma. The method was validated for ibrutinib and PCI-45227 over the concentration range of 0.500 to 100 ng/mL. The plasma concentration of ibrutinib and the major metabolite, PCI-45227, were determined. An ISR evaluation for method BTM-1792-R0, using samples selected from study 1127, was conducted and met the acceptance criteria.

Pharmacokinetic analysis

Plasma concentration data of ibrutinib and metabolite PCI-45227 from Arm A (ibrutinib + rituximab) and C (ibrutinib monotherapy) were analysed by non-compartmental methods using validated Phoenix WinNonlin software (Version 6.3). Blood samples were collected from all subjects pre-dose, at 1h (±15 min), 2h (±30 min), 4h (±30 min) and 6h (±1h) on week 4 (study day 22, treatment arm a and B) and week 5 (study day 29, treatment arm C).

All concentration values below the limit of quantitation were treated as 0 (zero) for pharmacokinetic analysis. Actual collection times relative to ibrutinib administration were used for the calculation of pharmacokinetic parameters. Pre-dose concentrations were applied as 24 hour concentrations in order to calculate steady-state pharmacokinetic parameters for Week 4, Day 22 (Arm A) and Week 5, Day 29 (Arm C). All mean concentration data were plotted using SigmaPlot (Version 12.0).

The metabolite-to-parent (M/P) ratio for AUC and Cmax AUC was also calculated (to evaluate the effect of CYP3A4 inhibitors) using the following formula: (AUCPCI-45227/MWPCI-45227) / (AUCibrutinib/MWibrutinib) where MW is the molecular weight.

Results

Pharmacokinetic analysis

Pharmacokinetic parameters of ibrutinib and metabolite PCI-45227 in individual subjects from Arm A (Week 4, Day 22) and Arm C (Week 5, Day 29) are presented in Table 2. Individual plasma concentration versus time profiles of ibrutinib and PCI-45227 in treatment arm A and C are illustrated in Figure 1.

Following once daily oral administration of 420 mg ibrutinib in combination with rituximab (treatment arm A, week 4, day 22), the inter-subject variability for exposure parameters was 60.2% for Cmax, 59.0% for AUC0-24h, and 59.2% for AUClast. Following once daily oral administration of 420 mg ibrutinib alone (treatment arm C, week 5, day 29), the inter-subject variability for exposure parameters was 51.9% for Cmax and 60.6% for AUC0-24h and AUClast.

Two subjects in treatment arm A and one subject in Arm C were co-administered with a moderate CYP3A inhibitor during the PK collection period. Due to a limited number of subjects with evaluable PK receiving moderate CYP3A inhibitors, the effect of moderate CYP3A inhibitor use on the pharmacokinetics of ibrutinib and PCI-45227 could not be evaluated.

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Table 3. Mean (SD) Pharmacokinetic Parameters of Ibrutinib and PCI-45227 in Plasma Following Once Daily Oral Dosing of 420 mg Ibrutinib in Subjects with Waldenstrom's Macroglobulinemia (WM)

Ibrutinib

Treatment	Week	Study Day	N	C_{max} (ng/mL)	t_{max}[a] (h)	t_{last}[a] (h)	AUC_{0-24h} (ng·h/mL)	AUC_{last} (ng·h/mL)	$t_{1/2,term}$ (h)	λ_z (1/h)	CL_{ss}/F (L/h)
Arm A (ibrutinib + rituximab)	4	22	63	121 (112)	1.98 (0.00, 6.00)	24.0[b] (6.00, 24.0)	781[b] (622)	781[b] (622)	5.79[c] (2.03)	0.132[c] (0.0407)	1468[b] (2497)
Arm C (ibrutinib monotherapy)	5	29	27	94.9 (76.1)	2.00 (0.580, 6.00)	24.0[c] (24.0, 24.0)	620[c] (424)	620[c] (424)	5.88[d] (1.91)	0.131[d] (0.0449)	1254[c] (1358)

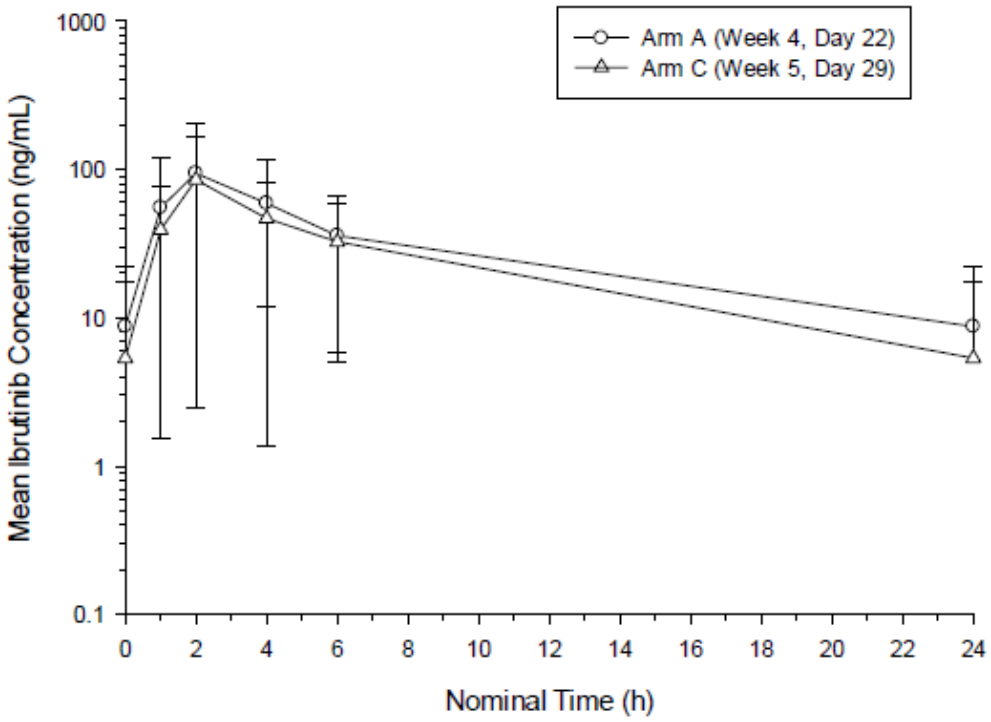
PCI-45227

Treatment	Week	Study Day	N	C_{max} (ng/mL)	t_{max}[a] (h)	t_{last}[a] (h)	AUC_{0-24h} (ng·h/mL)	AUC_{last} (ng·h/mL)	$t_{1/2,term}$ (h)	λ_z (1/h)	Metabolite/Parent Ratio C_{max}	Metabolite/Parent Ratio AUC_{0-24h}	Metabolite/Parent Ratio AUC_{last}
Arm A (ibrutinib + rituximab)	4	22	63	96.1 (57.9)	2.00 (0.00, 6.00)	24.0[b] (4.75, 24.0)	1101[b] (649)	1100[b] (651)	7.06[e] (1.90)	0.111[e] (0.0611)	1.24 (0.910)	1.71[b] (0.899)	1.73[b] (1.08)
Arm C (ibrutinib monotherapy)	5	29	27	98.7 (51.2)	2.08 (0.920, 6.00)	24.0[c] (24.0, 24.0)	1160[c] (703)	1160[c] (703)	6.37[f] (1.69)	0.116[f] (0.0283)	1.21 (0.642)	2.03[c] (1.22)	2.03[c] (1.22)

Abbreviations: N = number of subjects evaluable for PK analysis; C_{max} = observed maximum concentration; t_{max} = time to C_{max}; t_{last} = time of last measurable concentration; AUC = area under the concentration-time curve; $t_{1/2,term}$ = terminal elimination half-life; λ_z = terminal elimination rate constant; CL_{ss}/F = apparent total clearance at steady-state; SD = standard deviation
Metabolite/Parent Ratio (C_{max}) = ($C_{max,PCI-45227}/MW_{PCI-45227}$)/($C_{max,ibrutinib}/MW_{ibrutinib}$)
Metabolite/Parent Ratio (AUC) = ($AUC_{PCI-45227}/MW_{PCI-45227}$)/($AUC_{ibrutinib}/MW_{ibrutinib}$)
Molecular weight (MW): ibrutinib (440.50 g/mol); PCI-45227 (474.20 g/mol)
[a]Median (Min, Max) presented for t_{max} and t_{last}
[b]N=61; [c]N=25; [d]N=17; [e]N=29; [f]N=13

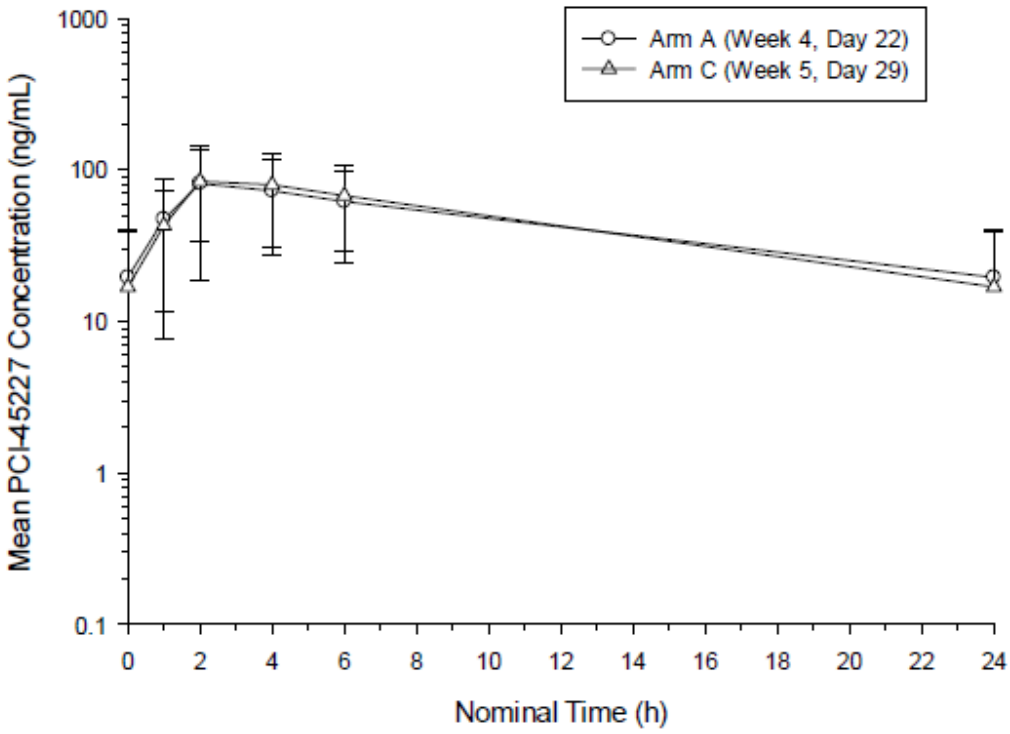
Figure 1. Mean Plasma Ibrutinib (A) and PCI-45227 (B) Concentration-Time Profiles (Semi-Log Scale) Following Once Daily Oral Administration of 420 mg Ibrutinib in Combination with Rituximab (Arm A, Subjects without CYP3A Inhibitor) or Ibrutinib Alone (Arm C) in Subjects with WM

A



B

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Ibrutinib steady-state PK parameters determined by non-compartmental analysis from Study 1127 were also compared with the observations obtained in subjects with chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) from Study 1102, where the ibrutinib administered dose was 420 mg/day. The results indicated that ibrutinib exposure in Study 1127 in subjects with WM was consistent with the previous studies with ibrutinib administered at 420 mg/day.

2.3.3. Pharmacodynamics

No additional data on pharmacodynamics are submitted in this application

2.3.4. Discussion on clinical pharmacology

The applicant performed a multicentre, randomized double-blind study of rituximab and ibrutinib or rituximab and placebo (Arm A and Arm B, respectively) in patients with Waldenström Macroglobulinemia. In addition the applicant performed an open-label sub-study (Arm C) where patients received Ibrutinib as monotherapy. Results from treatment Arm A were compared with treatment Arm C. Plasma samples were not analysed for rituximab plasma concentrations, therefore, only the effect of rituximab on ibrutinib could be assessed.

No tendencies towards clinically relevant PK-interactions of rituximab on ibrutinib could be observed. Mechanistically, no interaction between rituximab and ibrutinib is expected.

2.3.5. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:>

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2.4. Clinical efficacy

2.4.1. Dose response study(ies)

In an earlier study, study 1102, saturation of the BTK binding sites was confirmed at doses of 420 mg in the setting of CLL/SLL, why the 420 mg/day dosing regimen was chosen for ibrutinib in all subsequent clinical studies in WM (i.e. Studies 1118E and 1127). Ibrutinib monotherapy dosed 420 mg/day daily has demonstrated a favorable benefit/risk profile in subjects with previously treated WM, (study 1118E).

Ibrutinib at 420 mg/day, in combination with rituximab 375 mg/m2 intravenous (IV) has been shown to be a safe, well-tolerated and an active treatment regimen in high-risk CLL subjects.

2.4.2. Main study(ies)

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström Macroglobulinemia.

Methods

Study 1127 (iNNOVATE) was a randomized, double-blind, placebo-controlled Phase III study in subjects with treatment-naïve and previously treated WM who received ibrutinib (Arm A) or placebo (Arm B) in combination with rituximab to evaluate whether treatment with ibrutinib in combination with rituximab would result in an improvement in PFS compared with placebo in combination with rituximab.

In addition, Study 1127 included an open-label substudy (Arm C) to further investigate the safety and efficacy of ibrutinib monotherapy in subjects with WM who were considered refractory to the last prior rituximab-containing therapy. Inclusion of this open-label monotherapy substudy was suggested by the Scientific Advice Working Party (SAWP) during the Scientific Advice procedure EMEA/H/SAH/022/1/2013/II as means of obtaining data in patients with rapidly progressive disease who were refractory to rituximab.

Result from the earlier assessed 1118E study, ibrutinib monotherapy in previously treated WM, is presented below, in parallel with the results from the main study. A formal comparison of data between subjects who received ibrutinib as combination therapy with rituximab in the frontline setting with subjects who received single-agent ibrutinib in the relapsed or refractory setting is not appropriate; however, for ease of review in this submission, the MAH has presented data from the randomized part of Study 1127, the open-label monotherapy substudy of Study 1127, and Study 1118E side-by-side in a non-pooled format.

Study participants

Eligibility Criteria

The eligibility criteria for Study 1127 fulfilled general requirements for establishing a study population reflective of the target patient population. Eligible subjects were ≥18 years of age, symptomatic requiring treatment, and were required to have, untreated **or** previously treated, WM. Exclusion criteria for this study were chosen based on common practice in oncology studies and the safety profile of ibrutinib.

The subject selection criteria in the protocol defined the patient population, who had symptomatic disease requiring treatment based on meeting at least 1 of the recommendations from the Second International Workshop on Waldenström Macroglobulinemia for requiring treatment. The patients were also required to meet all inclusion/exclusion criteria such as adequate hematological and organ function and no

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life-threatening illness, medical condition, or organ system dysfunction that allowed evaluation of the chemotherapy-free regimen (ibrutinib+rituximab) in this population.

Key inclusion criteria

Eligible subjects were ≥ 18 years of age with;

• Untreated WM or previously treated WM (previously treated subjects must have had documented disease

• Centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second IWWM.

• Measurable disease defined as serum monoclonal IgM > 0.5 g/dL,

• Symptomatic disease meeting at least 1 of the recommendations from the Second IWWM for requiring treatment. (See below).

• Adequate hematologic, hepatic, and renal function and prothrombin time/international normalized ratio levels as defined in the protocol,

• ECOG PS ≤ 2.

Key exclusion criteria included

• Known involvement of the central nervous system by WM

• Disease refractory to prior rituximab-containing therapy (defined as relapse after the last rituximab containing therapy < 12 months since last dose of rituximab), or failure to achieve at least an MR (≥ 25% reduction but < 50% of serum IgM from baseline) after the last rituximab-containing therapy,

• Rituximab treatment within the last 12 months before the first dose of study drug.

• Subjects with a history of stroke or intracranial hemorrhage within 12 months prior to enrollment, or with clinically significant cardiovascular disease, or known bleeding disorder

Open-label Substudy

Eligible subjects must have met the inclusion criteria for the randomized study, and in addition, had disease that was refractory to the last prior rituximab-containing therapy (defined as either relapse after the last rituximab-containing therapy < 12 months since last dose of rituximab, or failure to achieve at least an MR after the last rituximab-containing therapy).

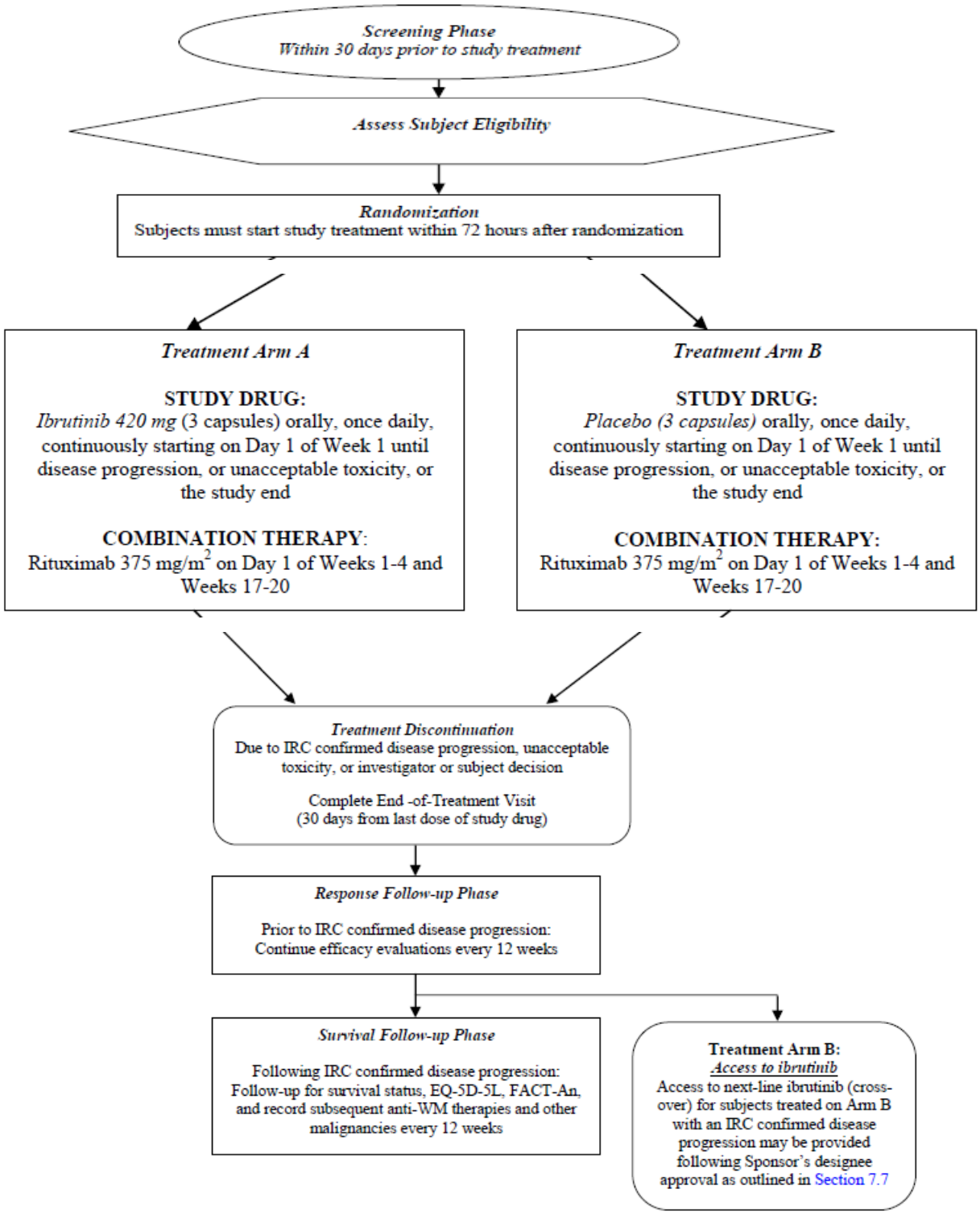
The exclusion criteria were identical to those for the randomized study except for those criteria related to prior rituximab use (outlined above for the randomized study), which did not apply to the open-label substudy.

Symptomatic disease was defined by constitutional symptoms (recurrent fever, night sweats, fatigue due to anemia, or weight loss); Presence of progressive, symptomatic lymphadenopathy or splenomegaly; anaemia (haemoglobin value of <or= 10 g/dL) due to marrow infiltration; Platelet count < 100 x 10^9/L due to marrow infiltration; Complications such as IgM-related hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia may also be indications for therapy.

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Treatments

Figure 2: Study schema, randomised part of study



Open-label Substudy

Ibrutinib 420 mg (3 capsules) was to be orally administered daily beginning Day 1 of Week 1.

All subjects in Arms A and B received rituximab and followed the package insert for rituximab dosing and toxicity management.

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Co-administration with strong or moderate CYP3A inhibitors was to be avoided during the study. If a strong CYP3A inhibitor was used, the ibrutinib dose was to be reduced to 140 mg or treatment withheld temporarily for the duration of the inhibitor use. Any chemotherapy, anti-cancer immunotherapy, experimental therapy, or radiotherapy was prohibited during the treatment phase of the study.

Objectives

The primary objective was to evaluate the effect of the addition of ibrutinib to rituximab on PFS assessed by an independent review committee (IRC) in subjects with WM. Efficacy evaluations were to be based on the modified Consensus Response Criteria from the VIth International Workshop on Waldenstrom's macroglobulinemia (IWWM).

Outcomes/endpoints

Primary Endpoint

Progression-free survival (PFS), as assessed by the IRC based on the modified Consensus Response Criteria from the VIth International Workshop for WM.

Secondary Endpoints

Secondary endpoints which will be tested include the following:

- Overall response rate (ORR) assessed by IRC (≥ partial response [PR]; according to the modified VIth IWWM criteria).
- Time to next treatment (TTnT)
- Rate of sustained Hgb improvement.
- Proportion of subjects with ≥ 3 points increase from baseline by Week 25 in FACIT-fatigue experience score from the FACT-An 5 items assessing fatigue symptoms.
- Overall survival (OS), planned OS would not be tested at the interim analysis.

Safety Endpoints

Safety endpoints include adverse events, clinical laboratory tests, vital signs and eye-related symptoms.

Exploratory Endpoints

PFS by investigator (INV), ORR (INV), time to sustained Hgb improvement, DOR (IRC and INV), CRR(IRC and INV), medical resource utilization (MRU), IgM, Hgb, lymph nodes and spleen measures, tumor involvement of bone marrow, EQ-5D-5L visual analog scale and utility score, FACTAn total score and subscale scores.

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Table 4: Modified 6th WM Response Criteria (NCCN 2014) for Investigator Assessment

Modified WM Response Criteria for Investigator Assessment of Response and Progression*	
Category	**Response Criteria**
Complete Response (CR)	• Serum IgM values in normal range • Disappearance of monoclonal protein by immunofixation *Note: Reconfirmation of CR status is required with a second immunofixation at any time point* • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy[4]/splenomegaly if present at baseline
Very Good Partial Response (VGPR)	• At least 90% reduction of serum IgM from baseline or serum IgM values in normal range • Reduction in lymphadenopathy[4]/splenomegaly if present at baseline
Partial Response (PR)	• At least 50% reduction of serum IgM from baseline • Reduction in lymphadenopathy[4]/splenomegaly if present at baseline
Minor Response (MR)	• At least 25% but <50% reduction of serum IgM from baseline
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease (PD)
Progressive Disease (PD)	At least one of the following • A ≥25% increase in serum IgM with a total increase of at least 500 mg/dL from nadir[1] ○ Confirmation of the initial IgM increase is required when IgM is sole criterion for progressive disease. • Appearance of a new lymph nodes > 1.5 cm in any axis, ≥50% increase from nadir in sum of product of diameters (SPD) of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis[2] • Appearance of new splenomegaly or ≥50% increase from nadir in enlargement of the spleen[2] • Appearance of new extranodal disease [2/3] • New or recurrent involvement in the bone marrow • New symptomatic disease on the basis of malignant pleural effusion, Bing Neel (WM CNS disease) syndrome, amyloidosis or light chain deposition disease, or other paraprotein mediated disorder.

1. Nadir for serum IgM is defined as the lowest serum IgM value obtained at any time from baseline onwards with the exception that serum IgM levels post-plasmapheresis will not be considered for up to 35 days.
2. For additional clarification to assess the appearance or progression of existing nodal and extranodal disease (Refer to Section 7.5.4.)
3. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease.
4. Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node

* The primary efficacy evaluations are based on IRC evaluation. In addition, eligibility for potential next-line therapy with ibrutinib will be based on IRC confirmed progression. The IRC assessment will incorporate assessments from the central radiology review and the details regarding the IRC evaluation for response and progression will be outlined in a separate charter.

Efficacy evaluation included the following components: Hematologic parameters by complete blood count; quantitative IgM serum immunoglobulins; quantitative serum-M protein; qualitative serum immunofixation / radiographic evaluation / bone marrow aspirate and biopsy (if applicable).

Determination of progression for the purpose of the primary efficacy endpoint was to be performed by the IRC. The IRC was established to conduct progression and response assessments centrally according to the committee's charter, and for subjects with nodal/extranodal disease at screening, to determine imaging requirements for the subject at follow-up visits.

The safety and the interim analysis of this study were monitored by an independent DMC.

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Key efficacy endpoints, definitions and analysis methods-Randomized study

Endpoint	Definition	Analysis Methods
Primary Endpoint		
PFS assessed by IRC	Time from the date of randomization to the date of first IRC-confirmed progressive disease or date of death due to any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy prior to documented progressive disease or death. For subjects who did not have IRC-confirmed progressive disease and not known death as of clinical data cutoff, PFS was censored at the date of the last evidence of no progression by IRC.	The treatment effect of Ibr+R compared to Pbo+R was tested with a stratified log rank test adjusted for 2 randomization stratification factors. The hazard ratio and its 95% CI based on a Cox regression model stratified by the 2 randomization stratification factors was calculated. Kaplan-Meier analysis for PFS distribution; median PFS estimated with 2-sided 95% CI. Sensitivity Analyses • Subjects who received subsequent antineoplastic therapy were censored at the last disease assessment showing no evidence of progressive before the use of subsequent therapy: same analyses as above. • Subjects who missed ≥2 consecutively planned disease assessments immediately before IRC-confirmed progressive disease or death were censored at the last disease assessment prior to documented progressive disease or death: same analyses as above. • Investigator assessed PFS: same analyses as above. • IRC-assessed PFS by unstratified log-rank test and unstratified Cox regression model. Subgroup Analyses Hazard ratio and its 95% CI based on unstratified Cox regression model for each subgroup.
Secondary Endpoints		
Response rate assessed by IRC	Proportion of subjects achieving a best overall response of confirmed CR, VGPR, or PR per the IRC assessment at or prior to initiation of subsequent antineoplastic therapy.	Response rate was compared between the two randomized treatment arms (Ibr+R vs. Pbo+R) using CMH chi-square test, adjusted for the 2 randomization stratification factors. 95% CI for the rate ratio was calculated. Sensitivity Analyses Investigator assessed response rate: same analyses as above. Subgroup Analyses Rate difference and its 95% CI for each subgroup of selected variables (eg, prior treatment history, MYD88 L265P mutational status).

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TTnT	Time from the date of randomization to the start date of any subsequent WM treatment. Subjects without subsequent treatment were censored at the date of the last study visit.	Same as PFS: stratified log-rank test, stratified Cox regression model, and Kaplan-Meier analysis.
Rate of sustained Hgb improvement	Proportion of subjects achieving a sustained improvement in Hgb at or prior to initiation of subsequent antineoplastic therapy. Hgb improvement was defined as an increase of ≥ 2 g/dL over baseline regardless of baseline value, or an increase to > 11 g/dL with a ≥ 0.5 g/dL improvement if baseline is ≤ 11 g/dL. Sustained Hgb improvement was defined as improvement that was sustained continuously for ≥ 56 days (8 weeks) without blood transfusion or growth factors.	The two randomized treatment arms were compared (Ibr+R vs. Pbo+R) using chi-square test. 95% CI for the rate ratio was calculated. Subgroup Analysis Chi-square test for subjects with Hgb ≤ 11 g/dL at baseline.
Proportion of subjects with ≥ 3 points increase from baseline by Week 25 in the FACIT-Fatigue subscale score (Appendix 9 Addendum)	Proportion of subjects with a ≥ 3 points increase from baseline in the 13-item FACIT-Fatigue subscale score at any time point at or prior to initiation of subsequent antineoplastic therapy by Week 25 (Appendix 9 Addendum).	The two randomized treatment arms were compared using CMH chi-square test, adjusting for the 2 randomization stratification factors. 95% CI for the rate ratio was calculated (Appendix 9 Addendum).
OS	Time from the date of randomization to the date of death from any cause. For subjects who were not known to have died at or prior to the clinical cutoff date, OS was censored on the date last known alive.	Unstratified log-rank test, unstratified Cox regression model, and Kaplan-Meier analysis. Exploratory analysis adjusting the crossover effect could be performed, if needed.

Sample size

Randomized Study

The 1127 study was designed to evaluate the effect of treatment on PFS and was powered for this endpoint. The sample size and power calculations were based on a 2-sided log-rank test for PFS and the following considerations: 1:1 randomization ratio between 2 treatment arms; target HR of 0.5 which corresponds to a 2-fold increase in median PFS for Ibr+R arm relative to the Pbo+R arm (median PFS 30 months vs. 15 months) with exponential distribution for PFS; minimum 80% power; 2-sided overall significance level of 0.05; and 1 interim analysis at 70% information (~50 PFS events).

Open-label Substudy

The sample size for the substudy was not determined according to statistical calculation. Thirty-one subjects were enrolled in the substudy.

Randomisation and Blinding (masking)

Patients were centrally randomized in study 1127. The treatment assignment was stratified using the following factors:

· WM IPSS assessed at screening (low vs. intermediate vs. high).

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· Number of prior systemic treatment regimens (0 vs. 1-2 vs. ≥ 3).

· ECOG PS (0-1 vs. 2).

The subjects were randomly assigned in a 1:1 ratio to each of the 2 treatment arms (Ibr+R arm, Pbo+R arm) within each randomization stratum. This randomization scheme was implemented within the interactive web response system (IWRS) based on information entered by clinical site staff at time of randomization. The subjects, investigators, and the Sponsor's study team members were blinded to treatment assignment.

Table 5: Subgroups for analyses in the Randomised study

Subgroup	Definition of Subgroup	Analysis Type[a]
Age	< 65, ≥ 65	D, E, S
Sex	Male, Female	D, E, S
Prior treatment history as recorded on CRFs	Previously untreated, Previously treated	D, E, S
Race	White, Non-White	E
Geographic region	US, Non-US	E
Baseline ECOG as recorded on CRFs	0-1, 2	E
Baseline IgM	< 40, ≥ 40 g/L	E
Baseline Hgb	≤ 11, > 11 g/dL	E
Baseline β2-microglobulin	≤ 3, > 3 mg/L	E
WM IPSS as recorded on CRFs	Low, Intermediate, High	E
MYD88 L265P mutational status	Mutated, No mutation	E
Baseline creatinine clearance	< 60, ≥ 60 mL/min	S
Baseline liver function based on NCI criteria	Normal, Abnormal (Mild, Moderate, Severe)	S

CRFs: case report forms; ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; IgM: immunoglobulin M; IPSS: International Prognostic Scoring System; IWRS: Interactive Web Response System; NCI: National Cancer Institute; US: United States; WM: Waldenstrom's macroglobulinemia.

[a] D = demographic and baseline disease characteristics
E = efficacy
S = safety (adverse events)

Statistical methods

The primary analysis of efficacy and safety, with the data extract completed on 17 October 2017 represented a pre-specified interim analysis for the randomized study was planned for 50 IRC confirmed PFS events and the final analysis was planned for 71 PFS events.

The interim analysis was based on a group sequential design with Lan-DeMets spending function with O'Brien-Fleming boundary. Using the above assumptions and based on an estimated accrual rate of approximately 12 subjects per month, the study was to enroll approximately 150 subjects (about 75 subjects to each arm) to observe 71 events in approximately 27 months from the first subject randomized. The interim analysis was conducted with 56 IRC-confirmed PFS events representing 79% of the planned total PFS events. Significance level of 2-sided alpha 0.023 for the interim analysis was determined based on the actual number of IRC-confirmed PFS events using O'Brien-Fleming boundary. This interim analysis crossed the superiority boundary and therefore is considered as the primary PFS analysis for the study, triggered by DMC recommendation after the review of interim efficacy analysis results.

Two of the 3 randomization stratification factors, WM IPSS (low, intermediate, high), and number of prior systemic treatment regimens (0, ≥ 1), were used for stratified analyses/tests. Progression-free survival per IRC assessment was summarized for each treatment arm using Kaplan-Meier (KM) estimates and compared using a stratified log-rank test. Hazard ratio (HR) (Ibr+R/Pbo+R) and its 95% confidence

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interval (CI) based on a Cox regression model stratified by the 2 randomization stratification factors were calculated.

The primary endpoint reached statistical significance, therefore tests of secondary endpoints were performed at the 2-sided significance level of 0.05 in a hierarchical order based on a closed testing procedure: 1) response rate, 2) TTnT, 3) rate of sustained Hgb improvement, and 4) proportion of subjects with ≥ 3 points increase from baseline by Week 25 in the FACIT-Fatigue subscale score. As planned, OS was not tested at the interim analysis and will be tested at the time of the final analysis.

For the open-label substudy, efficacy outcomes were analyzed separately from the randomized study. Times to event variables were analyzed using KM estimate. For categorical variables, 95% CIs were calculated based on the exact binomial distribution.

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Results

Participant flow

Table 6: Subject disposition-Randomized Study (ITT population)

	Ibr+R (N=75) n (%)	Pbo+R (N=75) n (%)	Total (N=150) n (%)
Disposition of Study Treatment Phase			
Ibrutinib/placebo disposition			
Did not receive study drug	0	0	0
Discontinued	19 (25.3)	49 (65.3)	68 (45.3)
Ongoing[a]	56 (74.7)	26 (34.7)	82 (54.7)
Primary reason for discontinuation of ibrutinib/placebo			
Progressive disease	7 (9.3)	33 (44.0)	40 (26.7)
Adverse event	4 (5.3)	3 (4.0)	7 (4.7)
Withdrawal by subject	6 (8.0)	7 (9.3)	13 (8.7)
Investigator decision	2 (2.7)	6 (8.0)	8 (5.3)
Rituximab disposition			
Did not receive rituximab	0	0	0
Discontinued	5 (6.7)	22 (29.3)	27 (18.0)
Completed[b]	70 (93.3)	53 (70.7)	123 (82.0)
Ongoing[a]	0	0	0
Primary reason for discontinuation of rituximab			
Progressive disease	0	6 (8.0)	6 (4.0)
Adverse event	2 (2.7)	9 (12.0)	11 (7.3)
Withdrawal by subject	3 (4.0)	4 (5.3)	7 (4.7)
Investigator decision	0	3 (4.0)	3 (2.0)
Disposition of Follow-up Phase			
Subject status			
In treatment phase	56 (74.7)	26 (34.7)	82 (54.7)
In follow-up[c]	13 (17.3)	38 (50.7)	51 (34.0)
Off study	6 (8.0)	11 (14.7)	17 (11.3)
Crossover to ibrutinib		30 (40.0)	
Death after crossover		2 (2.7)	
Primary reason for discontinuation of study			
Death	3 (4.0)	6 (8.0)	9 (6.0)
Lost to follow-up	0	1 (1.3)	1 (0.7)
Withdrawal of consent	3 (4.0)	4 (5.3)	7 (4.7)

Ibr+R: ibrutinib and rituximab; ITT: Intent-to-Treat; Pbo+R: placebo and rituximab.

[a] Subjects who received study treatment and had no treatment discontinuation information in the database are included in this category.

[b] Subject completed protocol specified treatment regimen.

[c] For Pbo+R arm, this category includes subjects who were randomized to Pbo+R, discontinued placebo and rituximab treatment, and had not exited the study.

Recruitment

The study 1127 enrolled patients from 9 countries (45 sites).

Study initiation date was 07 July 2014 and the provided CSR is based on database extraction, completed on 17 October 2017.

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Conduct of the study

There were 3 main amendments and 1 country-specific amendment to the original protocol (UK only). Key changes in the amendments are summarized here.

Table 7: Protocol amendments

Amendment Number and Date	Key Changes
1 07 March 2014	• Added open-label substudy treatment arm for subjects refractory to the last prior rituximab-containing therapy in alignment with the scientific advice received from the European Medicines Agency (subjects not suitable for Ibr+R or Pbo+R treatment in the randomized study may be enrolled into the substudy to received single-agent ibrutinib), with efficacy and safety to be descriptively summarized and analyzed separately from the randomized treatment arms. • Revised inclusion criteria to allow ECOG PS status of 2. • Changed a randomization factor from prior rituximab exposure (yes vs. no) to ECOG PS (0-1 vs. 2) to ensure treatment balance for subjects with ECOG PS of 2. • Changed FACT-An from a secondary to an exploratory objective.
2 09 February 2015	• Allowed inclusion of subjects with untreated WM. • Updated the number of prior systemic treatment regimens for stratification from 1-2 vs. ≥3 to 0 vs. 1-2 vs. ≥3 to maintain balance between the 2 randomized treatment arms with regard to the addition of previously untreated subjects. • Revised the O'Brien-Fleming boundary from 60% (~42 PFS events) to 70% (~50 PFS events) for the interim analysis for the randomized arms. • Added new or additional guidance or information on the use of anticoagulants, antiplatelets, prednisone or equivalent, P-glycoprotein substrates, dose modifications for subjects with hepatic impairment, and major hemorrhage.
2.1 02 June 2015 (UK only)	• Added more detailed guidance on the appropriate measures to avoid pregnancy.
3 09 October 2015	• Updated enrollment criteria to allow for the inclusion of subjects with abnormal coagulation results *unrelated to coagulopathy or bleeding disorders due to interfering substances*. • Clarified enrollment criteria abstinence language. • Updated enrollment criteria for next-line ibrutinib therapy to allow involvement of CNS by WM. • Added planned subgroup analyses to be conducted for the PFS primary efficacy endpoint. • Updated risk sections and CYP3A section to align with current version of IB.

CNS: central nervous system; CYP3A: cytochrome P450 3A; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; FACT-An: Functional Assessment of Cancer Therapy-Anemia; IB: investigator's brochure; Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab; PFS: progression-free survival; UK: United Kingdom; WM: Waldenstrom's macroglobulinemia.

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Table 8: Important deviations (Randomized ITT population)

Category	Ibr+R (N=75)	Pbo+R (N=75)	Total (N=150)
Total	0	5 (6.7%)	5 (3.3%)
Study Drug Administration	0	1 (1.3%)	1 (0.7%)
Enrollment/Randomization	0	3 (4.0%)	3 (2.0%)
Inclusion/Exclusion	0	1 (1.3%)	1 (0.7%)

Ibr+R: ibrutinib and rituximab; ITT: Intent-to-Treat; Pbo+R: placebo and rituximab.

Table 9: Ibrutinib or Placebo exposure-Randomized study

	Ibr+R (N=75)	Pbo+R (N=75)
Study drug duration (month)[a]		
n	75	75
Mean (SD)	23.9 (7.89)	15.1 (10.18)
Median	25.8	15.5
Min, Max	1.0, 37.2	0.4, 34.3
< 3	3 (4.0%)	8 (10.7%)
3 – < 6	1 (1.3%)	12 (16.0%)
6 – < 12	2 (2.7%)	14 (18.7%)
12 – < 18	7 (9.3%)	10 (13.3%)
18 – < 24	21 (28.0%)	14 (18.7%)
≥24	41 (54.7%)	17 (22.7%)
Average daily dose (mg/day)[b]		
Mean (SD)	395.2 (40.63)	410.7 (23.77)
Median	411.2	418.3
Min, Max	192.2, 420.0	242.7, 430.2
Relative dose intensity (%)[c]		
Mean (SD)	94.1 (9.67)	97.8 (5.66)
Median	97.9	99.6
Min, Max	45.8, 100.0	57.8, 102.4
Subjects with dose reduction due to adverse event		
Dose reduced to 280 mg/day	7 (9.3%)	0
Dose reduced to 140 mg/day	6 (8.0%)	0
Any dose reduction	13 (17.3%)	0

Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab; SD: standard deviation.
[a] Calculated as (last dose date of study drug - first dose date of study drug +1)/30.4375.
[b] Calculated by total cumulative dose received (mg)/study drug duration (day).
[c] Calculated by average daily dose/420.

Rituximab Exposure (Safety population)

The median average daily dose of ibrutinib was 411.2 mg (418.3 in the placebo group). 17.3% of the subjects in the Ibr+R arm had any ibrutinib dose reduction.

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Baseline data

Table 10: Demographic characteristics - Randomized ITT population

	Ibr+R (N=75)	Pbo+R (N=75)	Total (N=150)
Age (Years)			
n	75	75	150
Mean (SD)	69.2 (10.90)	66.1 (11.10)	67.6 (11.08)
Median	70.0	68.0	69.0
Min, Max	36, 89	39, 85	36, 89
Age groups - n (%)			
<65 years	28 (37.3)	30 (40.0)	58 (38.7)
≥65 years	47 (62.7)	45 (60.0)	92 (61.3)
<75 years	45 (60.0)	55 (73.3)	100 (66.7)
≥75 years	30 (40.0)	20 (26.7)	50 (33.3)
Gender - n (%)			
Male	45 (60.0)	54 (72.0)	99 (66.0)
Female	30 (40.0)	21 (28.0)	51 (34.0)
Race - n (%)			
American Indian or Alaska Native	0	0	0
Asian	3 (4.0)	0	3 (2.0)
Black or African American	1 (1.3)	1 (1.3)	2 (1.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	58 (77.3)	60 (80.0)	118 (78.7)
Multiple	0	0	0
Unknown	13 (17.3)	14 (18.7)	27 (18.0)
Region - n (%)			
United States	9 (12.0)	10 (13.3)	19 (12.7)
Canada	10 (13.3)	5 (6.7)	15 (10.0)
Europe	45 (60.0)	49 (65.3)	94 (62.7)
Oceania	11 (14.7)	11 (14.7)	22 (14.7)

Ibr+R: ibrutinib and rituximab; ITT: Intent-to-Treat; Pbo+R: placebo and rituximab; SD: standard deviation.

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Table 11: Baseline Disease Characteristics - Randomized ITT Population

	Ibr+R (N=75)	Pbo+R (N=75)	Total (N=150)
Months from initial diagnosis to randomization			
n	75	75	150
Mean (SD)	63.3 (60.63)	71.7 (64.31)	67.5 (62.44)
Median	50.4	55.9	52.6
Min, Max	0.7, 257.2	0.5, 247.0	0.5, 257.2
WM IPSS score as reported on CRF – n (%)			
Low	15 (20.0%)	17 (22.7%)	32 (21.3%)
Intermediate	33 (44.0%)	28 (37.3%)	61 (40.7%)
High	27 (36.0%)	30 (40.0%)	57 (38.0%)
ECOG PS as reported on CRF – n (%)			
0	39 (52.0%)	37 (49.3%)	76 (50.7%)
1	32 (42.7%)	32 (42.7%)	64 (42.7%)
2	4 (5.3%)	6 (8.0%)	10 (6.7%)
Number of prior systemic treatment regimens as reported on CRF – n (%)			
0	34 (45.3%)	34 (45.3%)	68 (45.3%)
1-2	34 (45.3%)	36 (48.0%)	70 (46.7%)
≥ 3	7 (9.3%)	5 (6.7%)	12 (8.0%)
Serum IgM (g/L)			
n	75	75	150
Mean (SD)	34.2 (18.61)	33.6 (18.71)	33.9 (18.60)
Median	32.9	31.8	31.9
Min, Max	6.2, 77.6	5.9, 83.3	5.9, 83.3
> 70	2 (2.7%)	4 (5.3%)	6 (4.0%)
≤ 70	73 (97.3%)	71 (94.7%)	144 (96.0%)

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	Ibr+R (N=75)	Pbo+R (N=75)	Total (N=150)
Beta-2 microglobulin (mg/L)			
n	75	75	150
Mean (SD)	4.4 (3.47)	4.2 (1.81)	4.3 (2.76)
Median	3.4	3.9	3.7
Min, Max	1.37, 27.90	1.50, 11.60	1.37, 27.90
> 3	53 (70.7%)	55 (73.3%)	108 (72.0%)
≤ 3	22 (29.3%)	20 (26.7%)	42 (28.0%)
Cytopenia – n (%)			
Hgb ≤ 110 g/L	44 (58.7%)	50 (66.7%)	94 (62.7%)
Platelets ≤ 100 x 10^9/L	4 (5.3%)	7 (9.3%)	11 (7.3%)
ANC ≤ 1.5 x 10^9/L	4 (5.3%)	1 (1.3%)	5 (3.3%)
MYD88 mutation status – n (%)			
L265P	58 (77.3%)	58 (77.3%)	116 (77.3%)
WT	11 (14.7%)	9 (12.0%)	20 (13.3%)
Unknown	6 (8.0%)	8 (10.7%)	14 (9.3%)
CXCR4 mutation status – n (%)			
WHIM	26 (34.7%)	23 (30.7%)	49 (32.7%)
WT	43 (57.3%)	44 (58.7%)	87 (58.0%)
Unknown	6 (8.0%)	8 (10.7%)	14 (9.3%)
MYD88 and CXCR4 mutation status – n (%)			
$MYD88^{WT}/CXCR4^{WT}$	11 (14.7%)	9 (12.0%)	20 (13.3%)
$MYD88^{L265P}/CXCR4^{WT}$	32 (42.7%)	35 (46.7%)	67 (44.7%)
$MYD88^{L265P}/CXCR4^{WHIM}$	26 (34.7%)	23 (30.7%)	49 (32.7%)
Unknown/Unknown	6 (8.0%)	8 (10.7%)	14 (9.3%)

ANC: absolute neutrophil count; CRF: case report form; ECOG PS: Eastern Cooperative Oncology Group performance status; IPSS: International Prognostic Scoring System; Hgb: hemoglobin; IgM: immunoglobulin M; Ibr+R: ibrutinib and rituximab; ITT: Intent-to-Treat; Pbo+R: placebo and rituximab; SD: standard deviation; WHIM: Warts, Hypogammaglobulinemia, Infections, Myelokathexis; WM: Waldenstrom's macroglobulinemia; WT: wild type.

Baseline is defined as the last measurement taken on or prior to the first dose date of study treatment. Central lab data are used in this summary table.

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Table 12: Reasons for initiating treatment - ITT

Table 3: Reason for Initiating WM Treatment; ITT Analysis Set (Study PCYC-1127-CA)

	Treatment Naive	Refractory/Relapse
Analysis set: ITT	68	82
Any symptomatic disease criteria met	68 (100.0%)	82 (100.0%)
Constitutional symptoms	16 (23.5%)	32 (39.0%)
Weight loss [1]	11 (16.2%)	13 (15.9%)
Fever [2]	5 (7.4%)	3 (3.7%)
Night sweats [3]	11 (16.2%)	24 (29.3%)
Fatigue [4]	35 (51.5%)	56 (68.3%)
Hyperviscosity [5]	9 (13.2%)	10 (12.2%)
Lymphadenopathy [6]	5 (7.4%)	8 (9.8%)
Symptomatic hepatomegaly and/or splenomegaly and/or organ tissue infiltration	5 (7.4%)	4 (4.9%)
Peripheral neuropathy due to WM	13 (19.1%)	10 (12.2%)
Symptomatic cryoglobulinemia	2 (2.9%)	3 (3.7%)
Cold agglutinin anemia	0	3 (3.7%)
IgM related immune hemolytic anemia and/or thrombocytopenia	2 (2.9%)	2 (2.4%)
Nephropathy related to WM	2 (2.9%)	4 (4.9%)
Amyloidosis related to WM	0	2 (2.4%)
Hemoglobin <=10g/dL	27 (39.7%)	21 (25.6%)
Platelet count <100x10^9/L	4 (5.9%)	4 (4.9%)
Serum monoclonal protein >5g/dL, with or without overt clinical symptoms	16 (23.5%)	14 (17.1%)

WM = Waldenstrom's Macroglobulinemia.
[1] Unintentional weight loss >=10% within the previous 6 months prior to Screening.
[2] Fevers higher than 100.5 F or 38.0 C for 2 or more weeks prior to Screening without evidence of infection.
[3] Night sweats for more than 1 month prior to Screening without evidence of infection.
[4] Clinically relevant fatigue which is not relieved by rest due to WM.
[5] Symptomatic hyperviscosity or serum viscosity levels greater than 4.0 centipoises.
[6] Lymphadenopathy which is either symptomatic or bulky (>=5 cm in maximum diameter)

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Table 13: Reasons for initiating treatment- Randomized part of study - ITT

Table 14.1.2.4 Reason for Initiating WM Treatment
ITT Population

	Ibr+R (N=75) n(%)	Pbo+R (N=75) n(%)	Total (N=150) n(%)
Any symptomatic disease criteria met	75 (100.0)	75 (100.0)	150 (100.0)
Constitutional symptoms	19 (25.3)	29 (38.7)	48 (32.0)
Weight loss [1]	10 (13.3)	14 (18.7)	24 (16.0)
Fever [2]	3 (4.0)	5 (6.7)	8 (5.3)
Night sweats [3]	13 (17.3)	22 (29.3)	35 (23.3)
Fatigue [4]	42 (56.0)	49 (65.3)	91 (60.7)
Hyperviscosity [5]	9 (12.0)	10 (13.3)	19 (12.7)
Lymphadenopathy [6]	7 (9.3)	6 (8.0)	13 (8.7)
Symptomatic hepatomegaly and/or splenomegaly and/or organ tissue infiltration	2 (2.7)	7 (9.3)	9 (6.0)
Peripheral neuropathy due to WM	15 (20.0)	8 (10.7)	23 (15.3)
Symptomatic cryoglobulinemia	2 (2.7)	3 (4.0)	5 (3.3)
Cold agglutinin anemia	1 (1.3)	2 (2.7)	3 (2.0)
IgM related immune hemolytic anemia and/or thrombocytopenia	0	4 (5.3)	4 (2.7)
Nephropathy related to WM	3 (4.0)	3 (4.0)	6 (4.0)
Amyloidosis related to WM	2 (2.7)	0	2 (1.3)
Hemoglobin <=10g/dL	20 (26.7)	28 (37.3)	48 (32.0)
Platelet count <100x10^9/L	2 (2.7)	6 (8.0)	8 (5.3)
Serum monoclonal protein >5g/dL, with or without overt clinical symptoms	18 (24.0)	12 (16.0)	30 (20.0)

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Numbers analysed

Data from the randomized part of Study 1127, the open-label monotherapy substudy of Study 1127, and Study 1118E are presented side-by-side in a non-pooled format.

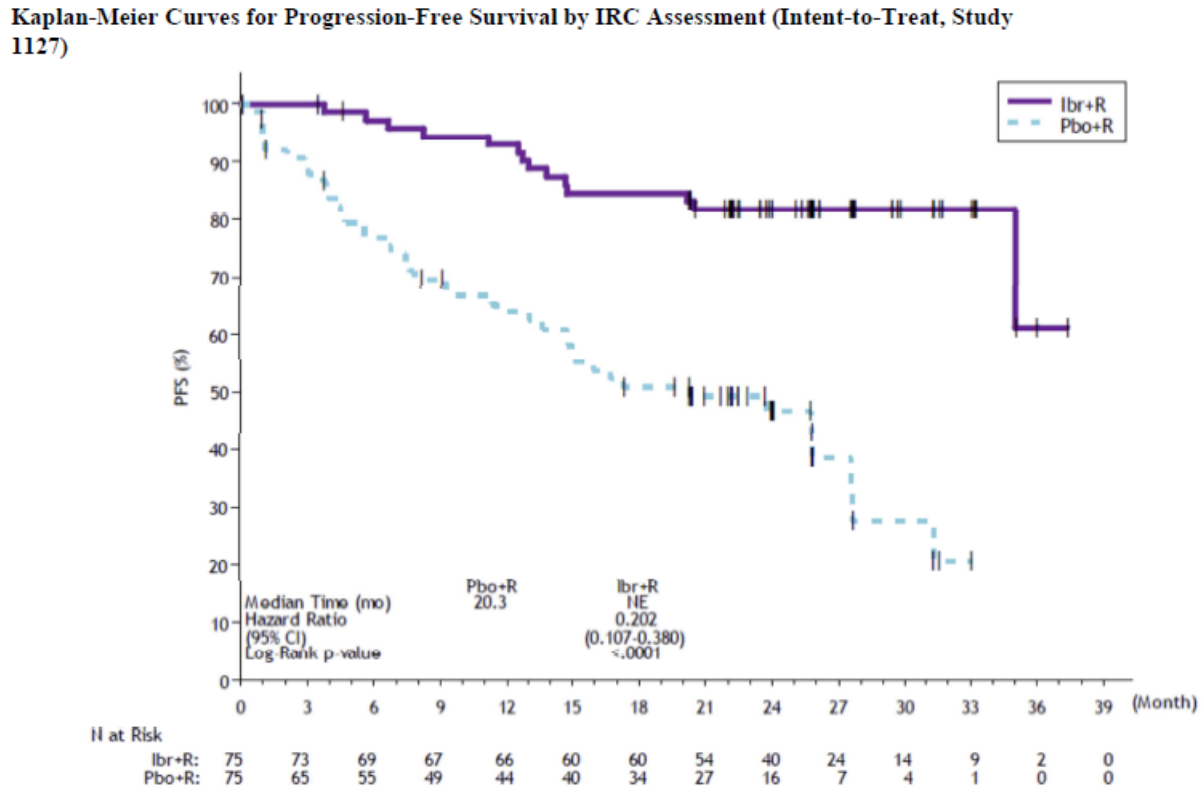
The interim analysis was conducted with 56 PFS events representing 79% of the planned total PFS events.

A total of 150 subjects were included in the randomised part in Study 1127 (75 patients in each arm) and 31 subjects were included in the monotherapy sub-study.

Outcomes and estimation

A formal comparison of data between subjects who received ibrutinib as combination therapy with rituximab in the frontline setting with subjects who received single-agent ibrutinib in the relapsed or refractory setting is not appropriate; however, for ease of review in this submission, the applicant has chosen to present

Figure 3: Primary endpoint: Progression free survival by IRC (Arm A and B)



CI=confidence interval; Ibr+R=ibrutinib and rituximab; IRC=Independent Review Committee; mo=month; N=number; NE=not estimable; Pbo+R=placebo and rituximab; PFS=progression-free survival

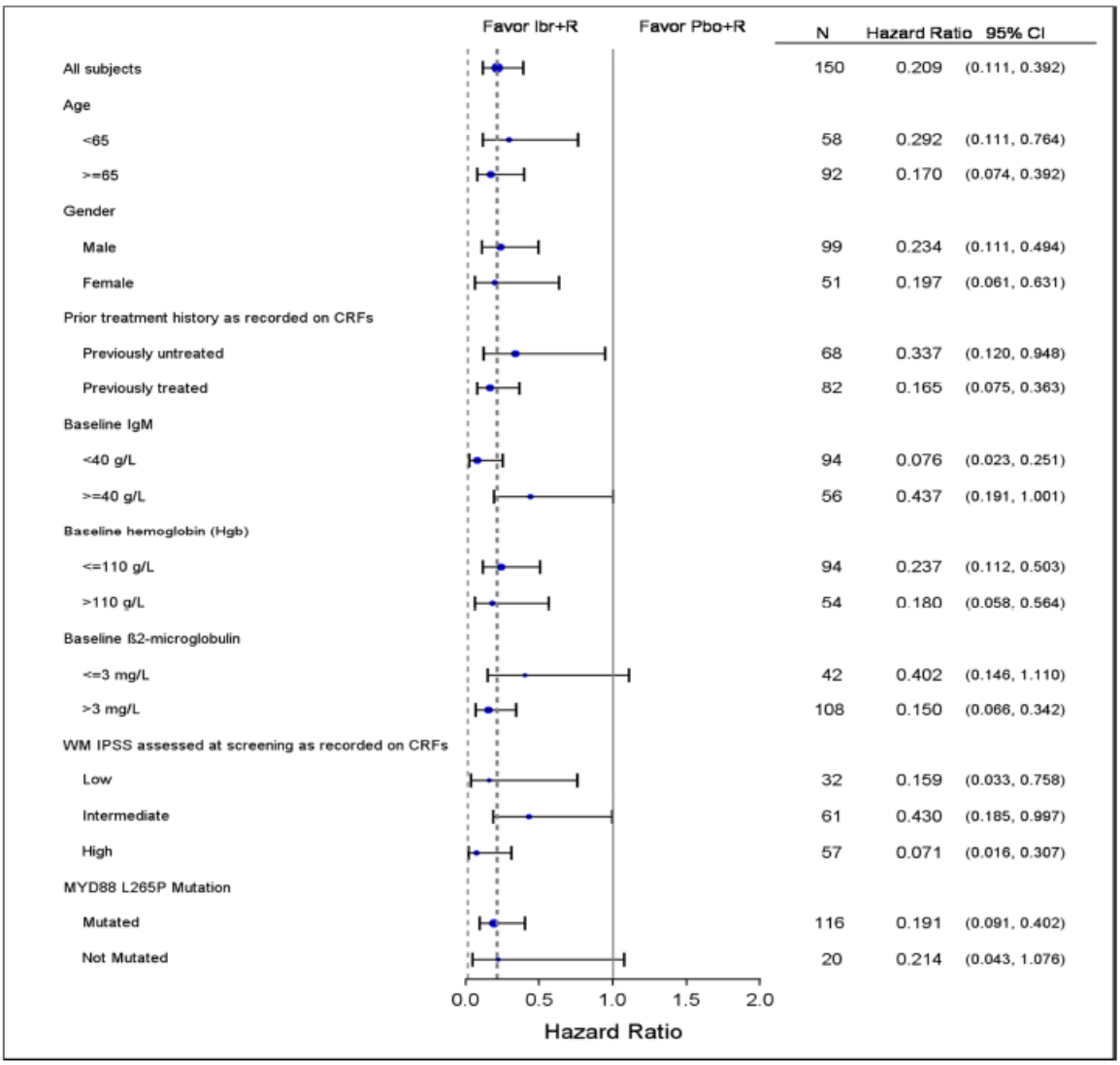
Median PFS per IRC assessment was not reached for the Ibr+R arm and was 20.3 months for the Pbo+R arm. The Kaplan-Meier point estimates of the PFS rate per IRC assessment at 30 months were 81.6% for the Ibr+R arm and 27.5% for the Pbo+R arm. This translates to a reduced the risk of progression or death by 80% for Ibr-R compared with Pbo+R; (HR=0.202; 95% CI: 0.107, 0.380; p <0.0001).

PFS per investigator assessment was consistent with the IRC assessment (HR=0.218; 95% CI: 0.118, 0.404; p <0.0001).

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Figure 4: PFS by subgroup

Progression-Free Survival by Subgroup Based on IRC Assessment– Study PCYC-1127-CA (Intent-to-Treat Population)



CI=confidence interval; CRF=case report form; Hgb=hemoglobin; Ibr+R=ibrutinib and rituximab; IgM=immunoglobulin M; IPSS=International Prognostic Scoring System; IRC=independent review committee; N=number; Pbo+R=placebo and rituximab; WM=Waldenstrom's macroglobulinemia

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Figure 5: PFS by IRC - ITT

Progression-free Survival Based on IRC Assessment – Randomized Study (ITT Population)

Progression free Survival (months)	Ibr+R (N=75)	Pbo+R (N=75)	Comparison/Difference Ibr+R vs. Pbo+R
Events - n (%)	14 (18.7)	42 (56.0)	
Disease progression - n	12	40	
Death - n	2	2	
Censored - n (%)	61 (81.3)	33 (44.0)	
Median (95% CI)[a]	NE (35.0, NE)	20.3 (13.7, 27.6)	
Min, Max	0.03+, 37.39+	0.53, 33.05+	
P value[b]			< 0.0001
Hazard ratio (95% CI)[c]			0.202 (0.107, 0.380)
PFS at landmark times - % (95% CI)[a]			
6 Months	97.2 (89.3, 99.3)	76.7 (65.2, 84.8)	20.5 (10.1, 31.0)
12 Months	93.0 (83.9, 97.0)	63.9 (51.6, 73.8)	29.1 (16.5, 41.7)
15 Months	84.5 (73.8, 91.1)	58.1 (45.8, 68.6)	26.4 (12.2, 40.7)
18 Months	84.5 (73.8, 91.1)	50.8 (38.7, 61.8)	33.7 (19.3, 48.1)
24 Months	81.6 (70.5, 88.9)	46.6 (34.2, 58.2)	35.0 (19.8, 50.1)
30 Months	81.6 (70.5, 88.9)	27.5 (12.8, 44.4)	54.1 (35.4, 72.9)

CI: confidence interval; Ibr+R: ibrutinib and rituximab; IPSS: International Prognostic Scoring System; IRC: independent review committee; ITT: Intent-to-Treat; IWRS: Interactive web response system; NE: not estimable; Pbo+R: placebo and rituximab; PFS: progression-free survival; WM: Waldenstrom's macroglobulinemia.

+ Indicates censored observation.

[a] Estimated by Kaplan-Meier method.

[b] P value is from stratified log-rank test.

[c] Hazard ratio is estimated using stratified Cox regression model.

The randomization stratification factors used in both stratified log-rank test and Cox regression model are WM IPSS (low, intermediate, high) and number of prior systemic treatment regimens (0, ≥1) as reported in IWRS.

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Table 14: Sensitivity analyses for PFS

Sensitivity Analyses for Progression-free Survival Based on IRC Assessment-Randomized Study (ITT Population)

Analysis	Ibr+R vs. Pbo+R	
	Hazard Ratio (95% CI)[a]	P value[b]
Unstratified analysis	0.209 (0.111, 0.392)	< 0.0001
Censoring at the last adequate response assessment prior to or on the date of initiating subsequent antineoplastic treatment	0.191 (0.101, 0.363)	< 0.0001
Censoring at the last adequate response assessment prior to documented progression or death for subjects who missed ≥2 consecutively planned disease assessments immediately prior to progression or death	0.202 (0.105, 0.391)	< 0.0001

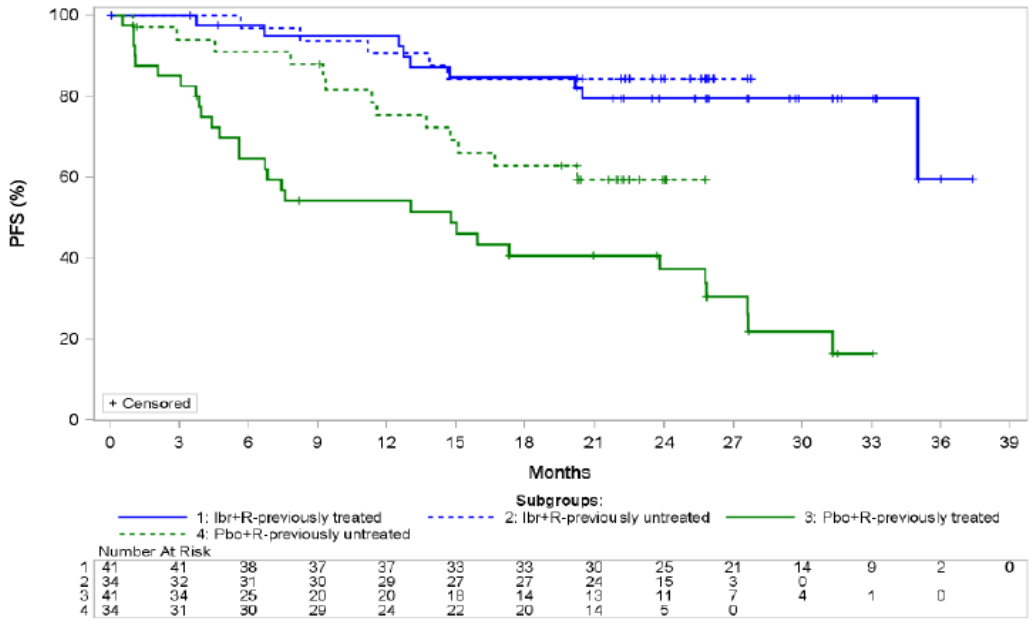
CI: confidence interval; Ibr+R: ibrutinib and rituximab; IPSS: International Prognostic Scoring System; IRC: independent review committee; IWRS: interactive web response system; ITT: Intent-to-Treat; IWRS: Interactive web response system; Pbo+R: placebo and rituximab; WM: Waldentrom's macroglobulinemia.

[a] Hazard ratio is estimated using stratified Cox regression model except for the unstratified analysis.

[b] P value is from stratified log-rank test except for the unstratified analysis.

The randomization stratification factors used in both stratified log-rank test and Cox regression model are WM IPSS (low, intermediate, high) and number of prior systemic treatment regimens (0, ≥ 1) as reported in IWRS.

Kaplan-Meier Curves for Progression-Free Survival Based on IRC Assessment by Prior Treatment History – Randomized Study (ITT Population)



Ibr+R: ibrutinib and rituximab; IRC: independent review committee; ITT: Intent-to-Treat; Pbo+R: placebo and rituximab; PFS: progression-free survival.

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Table 15: 25th and 75th percentiles at different landmarks

Table 5 below lists the different percentiles (25th and 75th percentiles), in addition to median PFS and PFS rate at different landmarks.

Table 5: Progression Free Survival (PFS) Based on IRC Assessment; ITT Analysis Set (Study PCYC-1127-CA)

	Ibr+R	Pbo+R	Comparison Ibr+R vs. Pbo+R
Analysis set: ITT	75	75	
Subjects randomized, n (%)	75 (100.0)	75 (100.0)	
PFS Events	14 (18.7%)	42 (56.0%)	
Disease Progression	12 (16.0%)	40 (53.3%)	
Death	2 (2.7%)	2 (2.7%)	
Censored	61 (81.3%)	33 (44.0%)	
25th percentile (months) (95% CI)	35.0 (14.7, NE)	6.8 (3.8, 11.6)	
Median (months) (95% CI)	NE (35.0, NE)	20.3 (13.7, 27.6)	
75th percentile (months) (95% CI)	NE (35.0, NE)	31.3 (25.8, NE)	
Range (months)	(0.03+, 37.39+)	(0.53, 33.05+)	
Hazard ratio (95% CI)[a]			0.202 (0.107, 0.380)
p-value[b]			<0.0001
Progression Free Survival			
12-month PFS rate (95% CI)	0.93 (0.84, 0.97)	0.64 (0.52, 0.74)	
18-month PFS rate (95% CI)	0.85 (0.74, 0.91)	0.51 (0.39, 0.62)	
24-month PFS rate (95% CI)	0.82 (0.70, 0.89)	0.47 (0.34, 0.58)	
30-month PFS rate (95% CI)	0.82 (0.70, 0.89)	0.27 (0.13, 0.44)	
36-month PFS rate (95% CI)	0.61 (0.20, 0.86)	NE (NE, NE)	

CI= confidence interval. + Indicates censored observation. NE= not estimable.
[a] Hazard ratio is estimated using stratified Cox regression model.
[b] P value is from stratified log-rank test.
The randomization stratification factors used in both stratified log-rank test and Cox regression model are WM IPSS (low, intermediate, high) and number of prior systemic treatment regimens (0, >=1) as reported in IWRS.

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Key secondary endpoint: Response rate (IRC)

Table 16: Response rate based on IRC assessment- Randomized study (ITT population)

	Ibr+R (N=75) n (%)	Pbo+R (N=75) n (%)	Ibr+R vs. Pbo+R
Response rate (CR, VGPR, PR)	54 (72.0)	24 (32.0)	
Rate ratio (95% CI)[a]			2.299 (1.592, 3.319)
P-value[a]			< 0.0001
Clinical response rate (CR, VGPR, PR, MR)	69 (92.0)	35 (46.7)	
Rate ratio (95% CI)[a]			2.001 (1.554, 2.576)
P-value[a]			< 0.0001
Best overall response			
Complete response (CR)	2 (2.7)	1 (1.3)	
Very good partial response (VGPR)	17 (22.7)	3 (4.0)	
Partial response (PR)	35 (46.7)	20 (26.7)	
Minor response (MR)	15 (20.0)	11 (14.7)	
Stable disease	2 (2.7)	31 (41.3)	
Progressive disease	0	7 (9.3)	
Not evaluable/Unknown	4 (5.3)	2 (2.7)	

CI: confidence interval; Ibr+R: ibrutinib and rituximab; IPSS: International Prognostic Scoring System; IRC: independent review committee; ITT: Intent-to-Treat; IWRS: interactive web response system; Pbo+R: placebo and rituximab; WM: Waldentrom's macroglobulinemia.

CR, VGPR, PR and MR required confirmation with 2 consecutive assessments.

[a] Rate ratio and p value are based on Cochran-Mantel-Haenszel chi-square test stratified by WM IPSS (low, intermediate, high) and number of prior systemic treatment regimens (0, ≥1) as reported in IWRS. Rate ratio >1 favors Ibr+R.

The IRC assessment incorporated assessments from the central radiology review. CR required complete resolution of lymphadenopathy/splenomegaly if present at baseline. VGPR and PR required reduction in lymphadenopathy/splenomegaly if present at baseline.

-The subgroup with previously untreated patients showed 70.6% and 47.1% response rate in Ibr+R and Pbo+R arms, respectively.

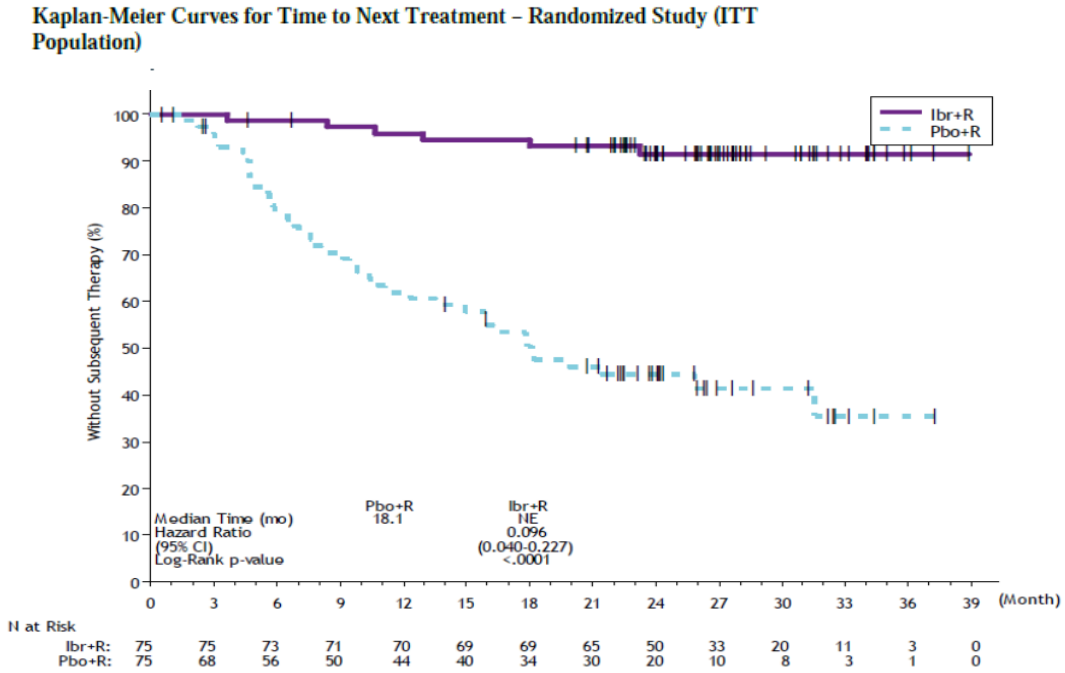
- The subgroup with previously treated patients showed 73.2% and 19.5% response rate in Ibr+R and Pbo+R arms, respectively.

- The clinical response rate (cRR: including MR as well as PR, VGPR and CR) was 91.2% and 58.8% in Ibr+R and Pbo+R arms, respectively.

-The response rate for subjects with and without the MYD88 ^{L265P} mutation was 75.9% and 63.6% for the Ibr+R arm and 36.2% and 22.2% for the Pbo+R arm.

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Figure 6: Key secondary endpoint:TTnT



CI: confidence interval; Ibr+R: ibrutinib and rituximab; ITT: Intent-to-Treat; mo: month; NE: not estimable; Pbo+R: placebo and rituximab.

Progression and symptomatic disease meeting criteria for requiring treatment had to be confirmed by IRC. Subjects in the Pbo+R arm could be eligible to receive Ibrutinib as next line of therapy (crossover).

Table 17: Key secondary endpoint: Rate of sustained Hgb improvement:

	Ibr+R n/N (%)	Pbo+R n/N (%)	Ibr+R vs. Pbo+R
All subjects	55/75 (73.3)	31/75 (41.3)	
Rate ratio (95% CI)[a]			1.774 (1.311, 2.400)
P value[a]			< 0.0001
Subjects with baseline Hgb ≤ 110 g/L	42/44 (95.5)	28/50 (56.0)	
Rate ratio (95% CI)[a]			1.705 (1.322, 2.197)
P value[a]			< 0.0001

CI: confidence interval; Hgb: hemoglobin; Ibr+R: ibrutinib and rituximab; ITT: Intent-to-Treat; Pbo+R: placebo and rituximab.
N: Number of subjects in the specified population, n: number of subjects with sustained Hgb improvement.
[a] Based on chi-square test.
Sustained hemoglobin improvement is defined as hemoglobin improvement that sustained continuously for ≥ 56 days without blood transfusion or growth factors which includes hemoglobin > 110 g/L with at least a 5 g/L improvement if baseline ≤ 110 g/L or increase ≥ 20 g/L over baseline.
Central lab data prior to or on the date of initiating subsequent antineoplastic therapy/crossover ibrutinib are used for this tabulation.

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Table 18: Proportion of sustained Hgb improvement. Previously untreated patients

	Ibr+R	Pbo+R	Ibr+R vs Pbo+R
	n/N (%)	n/N (%)	(%)
All subjects	26/34 (76.5)	19/34 (55.9)	
– Rate difference (95%CI)			20.6 (-4.6. 43.9)
– P value			0.1232
Subjects with baseline ≤ 110g/l	22/22 (100.0)	18/23 (78.3)	
– Rate difference (95%CI)			21.7 (-7.0. 48.7)
– P value			0.0491

Table 19: Proportion of sustained Hgb improvement. Previously treated patients

	Ibr+R	Pbo+R	Ibr+R vs Pbo+R
	n/N (%)	n/N (%)	(%)
All subjects	29/41 (70.7)	12/41 (29.3)	
– Rate difference (95%CI)			41.5 (19.3. 60.5)
– P value			0.0003
Subjects with baseline ≤ 110g/l	20/22 (90.9)	10/27 (37.0)	
– Rate difference (95%CI)			53.9 (27.0. 74.3)
– P value			0.0001

Key secondary endpoint: FACIT-Fatigue Subscale Score

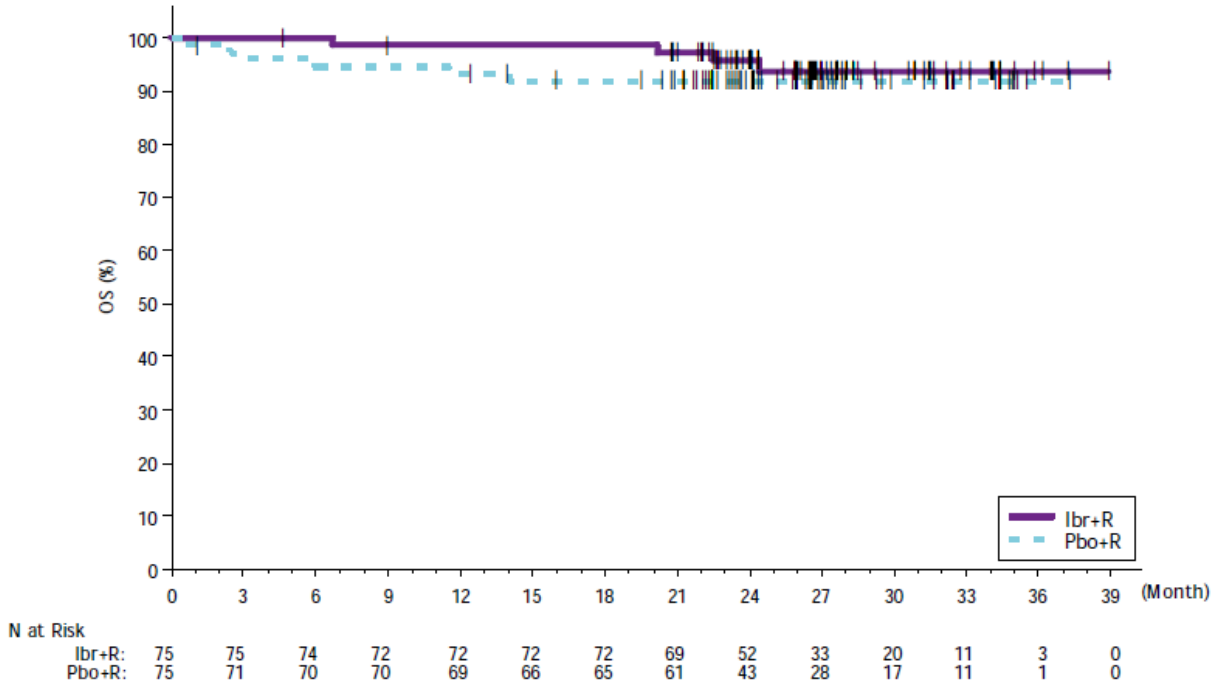
By week 25, 68.0% of subjects in the Ibr+R arm and 54.7% of subjects in the Pbo+R arm had a ≥ 3 points increase from baseline in the FACIT-Fatigue subscale score: rate ratio = 1.238 (95% CI: 0.955, 1.603), p = 0.1059.

Key secondary endpoint: Overall Survival

OS was formaly not tested due to the low number of events. The KM point estimate of OS rate at 30 months was 93.7% and 91.9% for the Ibr+R and Pbo+r respectively. At date of data lock there were 4 (5.3%) deaths inte the Ibr+R arm and 6 deaths (8.0%) in the Pbo-R arm.

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Figure 7: The K-M plot for OS (ITT population)



Exploratory analyses: Duration of respons (IRC and INV)

For responding patients, the median DOR was not reached for the Ibr+R arm while it was 21.2 months for the Pbo+R group. A landmark analysis at 24 months showed 92.2% for the Ibr+R arm and 40.8% for the Pbo-R arm.

As per investigator assessment, DOR was not reached for the Ibr+R arm, while it was 23 months for the Pbo+R group. Corresponding landmark analysis at 24 months was 89.0% versus 40.6%.

Exploratory analyses: Clinical response rate (INV)

In contrast to response rate (RR) the clinical response rate (CRR) also includes minor response rate (MR). The CRR was 92.0% for the Ibr+R arm vs. 46.7% for the Pbo+R arm.

- CRR for previously untreated patients was 91.2% for the Ibr+R arm and 58.8% for the Pbo+R arm, while CRR for previously treated patients was 92.7% for the Ibr+R arm and 36.6% for the Pbo+R arm.

- CRR for subjects with the MYD88 L265P mutation was 96.6% for the Ibr+R arm versus 48.3% for the Pbo+R arm. Corresponding CRR for subjects without MYD88 L265P mutation was 81.8% and 55.6%.

Exploratory analyses: Hemoglobin change over time

The median Hgb increased continuously from baseline and onwards in both arms. In the Ibr+R arm median baseline Hgb was 104.5 g/L and ranged between 129.5 to 133.0 during weeks 41-97, whereas the corresponding value in Pbo+R was 99.5 g/L (baseline) raising to 127.0 to 129.0 g/L (week 41-97).

Exploratory analyses: disease evaluations in other compartments

In study 1127, 56/75 and 58/75 patients in the Ibr+r and Pbo+R arms, respectively, presented with lymphadenopathy. Responding patients, in both treatment arms, showed reduction in lymph node volume and spleen size. The bone marrow compartment also showed a decreased percentage of

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lymphoplasmacytic cells in response to treatment, compared to baseline; the absolute number of patients in the Pbo+R arm that underwent a second bone marrow assessment was only 32 out of the 74 initial patients. The correponding numbers in the Ibr+R arm were 54/75.

Exploratory analyses:Medical resource utilisation

In the Ibr+R arm no patients had a plasmapheresis, while 12 subjects in the Pbo+R arm had at least one (median 3.5) plasmapheresis.

The median number of subjects hospitalized, the median number of hospitalizations and the number of subjects with emergency room visits were all higher in the Ibr+R arm as compared to the Pbo+R arm.

Exploratory analyses: Infusion related reactions

Infusion-related reactions of any grade (based on a custom SMQ) occurred in 48.0 % of subjects in the Ibr+R vs. 61.3 % of subjects in the Pbo+R arm. Grade 3 or higher event rates were 1.3 % vs. 16.0 % for the Ibr+R vs. Pbo+R arms, respectively.

Exploratory analyses:EQ-5D-5L Visual analog scale and*Exploratory analyses:FACT-An assessments*

The change from baseline in EQ-5D-5L visual analogue scale and utility score using the mixed model for repeated measures showed no differences between the treatment arms. The change from baseline in FACIT-Fatigue and FACT-An scores using the mixed model for repeated measures did not show any difference between the treatment arms.

Exploratory analyses: Biomarker

Apart from the PFS results and the RR reported for MYD88 ^{L265P} MYD88^{WT} presented above, data on the subgoups MYD88^{L265P}/CXCR4^{WT}, MYD88^{L265P}/CXCR4^{WHIM}, and MYD88^{WT}/CXCR4^{WT} was also presented. Among baseline samples from 150 subjects in the Ibr+R and Pbo+R arms, 136 samples provided assay results.

Table 20: Summary of mutation rate

Table 2 Summary of MYD88^{L265P} and CXCR4^{WHIM} mutation rate in tested samples

	Arms A and B (n*=136)	Arm C (n*=25)
MYD88^{L265P} Mutation		
Mutated	116, (85.29%)	24, (96%)
Wild-Type	20, (14.71%)	1, (4%)
CXCR4^{WHIM} Mutation		
Mutated	49, (36.03%)	7, (28%)
Wild-Type	87, (63.97%)	18, (72%)
MYD88^{L265P}/CXCR4^{WHIM} Mutation		
MYD88^{WildType}/CXCR4^{WildType}	20, (14.71%)	1, (4%)
MYD88^{L265P}/CXCR4^{WildType}	67, (49.26%)	17, (68%)
MYD88^{WildType}/CXCR4^{WHIM}	0, (0%)	0, (0%)
MYD88^{L265P}/CXCR4^{WHIM}	49, (36.03%)	7, (28%)

*number of tested samples in arms A and B or arm C.

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Table 21: PFS Based on IRC Assessment Subgroup Analysis ITT Population (PCYC-1127-CA, CSR)

	Ibr+R			Pbo+R			Ibr+R vs. Pbo+R
Subgroups	N	Event n (%)	Median (95% CI) [1] (Months)	N	Event n (%)	Median (95% CI) [1] (Months)	Hazard Ratio (95% CI) [2]
MYD88 L265P/CXCR4 WHIM							
MYD88WT/CXCR4WT	11	2 (18.2)	NE (5.7, NE)	9	6 (66.7)	23.8 (1.0, NE)	0.214 (0.043, 1.076)
MYD88MUT/CXCR4WT	32	4 (12.5)	NE (NE, NE)	35	18 (51.4)	17.3 (7.6, 31.3)	0.165 (0.055, 0.489)
MYD88MUT/CXCR4MUT	26	6 (23.1)	35.0 (NE, NE)	23	14 (60.9)	15.0 (9.2, NE)	0.237 (0.085, 0.662)

Open label sub-study

Thirty-one subjects were enrolled in the substudy and the median time on study was 34.4 months and the median duration of ibrutinib exposure was 33.1 months. The median average daily dose was 417.2 mg/day, and the median relative dose intensity was 99.3%. The majority of subjects (80.6%) were on ibrutinib for ≥ 24 months.

All treated subjects (same as safety population) include all subjects who received at least one dose of study drug.

Disposition of Study Treatment Phase - Open Label Substudy All Treated Subjects

Table 14.1.1.2.C Disposition of Study Treatment Phase - Open Label Substudy
All Treated Subjects

	Ibr (N=31) n(%)
Ibrutinib Disposition	
Did Not Receive Study Drug	0
Discontinued	14 (45.2)
Ongoing [1]	17 (54.8)
Primary Reason for Discontinuation of Ibrutinib	
Progressive Disease	10 (32.3)
Adverse Event	2 (6.5)
Withdrawal by Subject	2 (6.5)
Investigator Decision	0
Study Terminated by Sponsor	0

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Demographics, open label substudy

Table 14.1.2.1.C Subject Demographics - Open Label Substudy
All Treated Subjects

	Ibr (N=31)
Age (Years)	
n	31
Mean (SD)	66.4 (10.76)
Median	67.0
Min, Max	47, 90
Age groups - n (%)	
< 65 years	14 (45.2)
>= 65 years	17 (54.8)
< 75 years	24 (77.4)
>= 75 years	7 (22.6)
Gender - n (%)	
Male	20 (64.5)
Female	11 (35.5)
Race - n (%)	
American Indian or Alaska Native	0
Asian	2 (6.5)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	26 (83.9)
Multiple	0
Unknown	3 (9.7)
Ethnicity - n (%)	
Hispanic or Latino	1 (3.2)
Not Hispanic or Latino	30 (96.8)
Unknown	0

The median age was 67.0 years (1127 randomized part: 70.0 years).

The median time since diagnosis was 91 months, (1127 randomized part:53 months).

The reported WM IPSS score was; Low: 22.6% intermediate: 35.5% and high: 41.9% (1127 randomized part: Low: 21.3% intermediate: 40.7 % and high: 38.0%).

ECOG score 0:41.9%, 1: 38.7% and 2: 19.4 %. Compared to the randomized part where the corresponding score was 0:50.7%, 1: 42.7% and 2: 6.7%.

Number of prior treatments; 1-2: 29.0% ≥3: 71.0%, with a median of 4 (range 1-7). The most common reason for initiating treatment was constitutional symptoms, fatigue, Hgb <=10g/dL and lymphadenopathy. All patients had received rituximab the median number of prior rituximab therapies was 2 (range: 1 to 6). Medium number of prior treatments in the randomized part, study 1127, was 2.

MYD88 ^{L265P} mutations were present in 77.4% of subjects, absent in 1 subject, and 19.4% of subjects were not evaluable for mutation status.

One subject in the open-label substudy was reported with an important protocol deviation and it is unlikely to have affected the overall efficacy and safety results of the substudy.

*Primary endpoint: Progression free survival (**Arm C**, IRC and INV)*

The median PFS was not reached (IRC: 95% CI: 27.4, NE; INV: 95% CI: 27.6, NE). The Kaplan-Meier point estimates of the PFS rate per IRC and investigator assessment for the open-label monotherapy substudy were 80.6% and 87.1% at 18 months, respectively, and 57.5% (95% CI: 38.2, 72.7) and 64.4% (95% CI: 44.9, 78.4) at 30 months, respectively.

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Table 14.2.1.1.C Progression Free Survival (PFS) - Open Label Substudy
All Treated Subjects

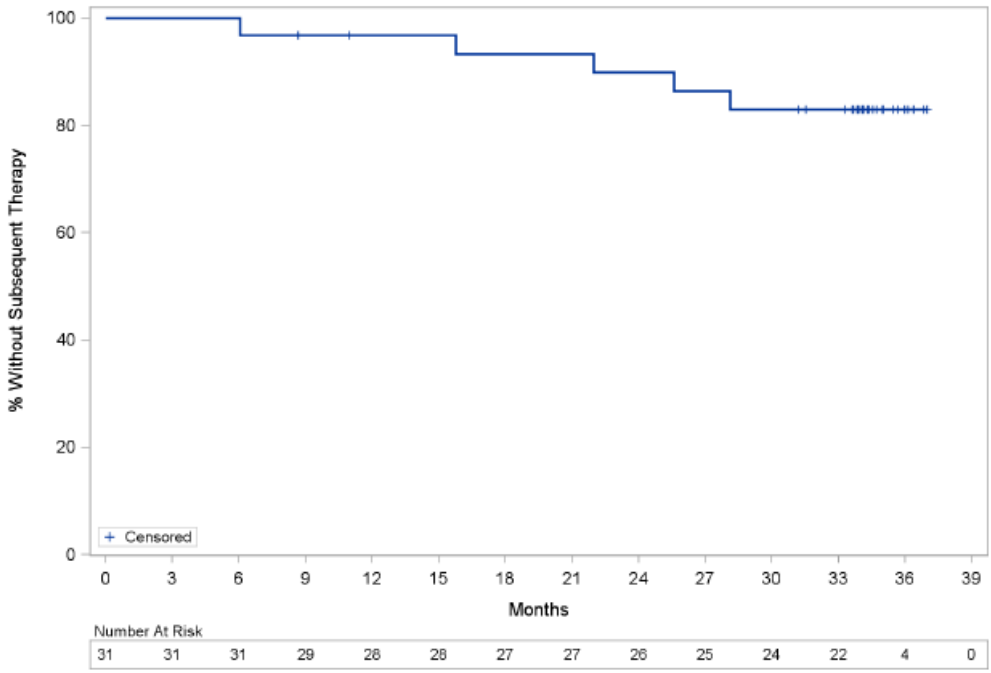
Progression Free Survival (Months)	IRC Assessment Ibr (N=31)	Investigator Assessment Ibr (N=31)
Events - n (%)	14 (45.2)	13 (41.9)
Disease Progression - n	13	12
Death - n	1	1
Censored - n (%)	17 (54.8)	18 (58.1)
Median (95% CI) [1]	NE (27.4, NE)	NE (27.6, NE)
Min, Max	2.79, 35.25+	5.62, 36.99+
PFS at landmark times - % (95% CI) [1]		
6 months	87.1 (69.2, 95.0)	93.5 (76.6, 98.3)
12 months	83.9 (65.5, 92.9)	93.5 (76.6, 98.3)
15 months	80.6 (61.9, 90.8)	87.1 (69.2, 95.0)
18 months	80.6 (61.9, 90.8)	87.1 (69.2, 95.0)
24 months	77.4 (58.4, 88.5)	83.9 (65.5, 92.9)
30 months	57.5 (38.2, 72.7)	64.4 (44.9, 78.4)
36 months		56.4 (36.7, 72.1)

*Secondary endpoints (**Arm C**, IRC and INV):*

Response rate (≥PR) per IRC was 71.0%, and per INV assessment 77.4%. The majority of responses were PR with no CR.

The median TTnT was not reached; at the 30-month landmark estimate 82.9% had not received subsequent treatment. Five of the 31 subjects received subsequent treatment.

Kaplan-Meier curve for TTnT



Hgb improvement was seen in 71% of the subjects and by week 25, 87% of the subjects had a ≥ 3 increase in FACIT-fatigue subscale score.

Median OS was not reached; the KM point estimate of the OS rate at 30 months was 90.3%.

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Ancillary analyses

Summary of main study(ies)

The following table summarizes data from the randomised part of Study 1127 (N=150 subjects; Treatment arm A and B), the open-label monotherapy substudy of 1127 (N=31 subjects; Treatment Arm C), as well as Study 1118E (N=63 subjects) are presented in a side by side format;

Table 1. Summary of Efficacy for trial 1127 and 1118E

	Study 1127 (Intent-to-Treat Population)		Single-agent Ibrutinib	
			Study 1127 Open-Label Substudy (All-treated Population)	Study 1118E (All-treated Population)
	Ibr+R (N=75)	Pbo+R (N=75)	Ibrutinib (N=31)	Ibrutinib N=63
Progression-free Survival per IRC (months)				
Median (95% CI)	NE (35.0, NE)	20.3 (13.7, 27.6)	NE (27.4, NE)	NE (NE, NE)
Min, Max	0.03+, 37.39+	0.53, 33.05+	2.79, 35.25+	0.03+, 19.94+
p-value	< 0.0001		NA	NA
Hazard Ratio (95% CI)	0.202 (0.107, 0.380)		NA	NA
Progression-free Survival per Investigator (months)				
Median (95% CI)	NE (35.0, NE)	20.3 (11.6, 31.3)	NE (27.6, NE)	NE (NE, NE)
Min, Max	3.45+, 37.16+	0.53, 33.05+	5.62, 36.99+	0.76, 19.94+
p-value	< 0.0001		NA	NA
Hazard Ratio (95% CI)	0.218 (0.118, 0.404)		NA	NA
Response Rate[a] (PR or better) per IRC (%)	72.0	32.0	71.0	61.9
p-value	< 0.0001		NA	<0.0001[b]
Rate ratio (95% CI)	2.299 (1.592, 3.319)		NA	NA
Clinical Response Rate[c] (MR or better) per IRC %	92.0	46.7	87.1	82.5
p-value	< 0.0001		NA	< 0.0001[b]
Rate ratio (95% CI)	2.001 (1.554, 2.576)		NA	NA
DOR (responders only) (PR or better) per IRC (months)				
n	54	24	22	39
Median (95% CI)	NE (NE, NE)	21.2 (20.3, 25.8)	NE (26.5, NE)	NE (NE, NE)
Min, Max	1.87+, 36.37+	4.63, 25.79	2.43, 34.23+	2.79+, 18.79+
Time to Next Treatment (months)				
Median (95% CI)	NE (NE, NE)	18.1 (11.1, NE)	NE (NE, NE)	
Min, Max	3.65, 38.90+	0.53+, 37.26+	6.05, 36.99+	NA
p-value	< 0.0001		NA	
Hazard Ratio (95% CI)	0.096 (0.040, 0.227)		NA	

Analysis performed across trials (pooled analyses and meta-analysis)

Updated results from Study 1118 were submitted as PAM (EMEA/H/C/3791) and are presented side by side with study 1127 in the efficacy assessment.

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Clinical studies in special populations

Please refer to subgroup analysis of PFS, on the age, gender and prior treatment status (previously treated or untreated) subgroups and in subjects with or without MYD88 mutation.

Supportive study

The previously submitted single-arm data from Study 1118E (N=63) is presented side by side to data from the present study 1127 (N=150) and the monotherapy substudy (31); allowing for the comparison of the efficacy of ibrutinib in combination with rituximab (Study 1127) or as a single agent. No formally integrated statistical analyses were performed.

2.4.3. Discussion on clinical efficacy

In the present CSR, key efficacy data from Study 1127 (n=150 for the randomized part [A and B], n=31 for the open-label monotherapy substudy [Arm C]) are presented and efficacy data from Study PCYC-1118E (hereafter referred to as study 1118E, N=63) are also presented as comparison. The earlier study 1118E was a single-arm, multicentre, Phase 2 study of single agent ibrutinib in adult subjects with previously treated WM, and forms the basis of the current approved WM indication in the EU SmPC.

Dose evaluation was presented in the previously assessed study 1118E. No new data is presented in the present CSR, which is acceptable.

Design and conduct of clinical studies

This application in WM is based on the results obtained in the phase 3 study 1127 consisting of a 2-armed randomised double blind study (n=150, Ibr+R vs Pbo+R) and a single arm study (n=31, monotherapy ibrutinib) with both untreated and previously treated WM (randomised part) and previously treated WM also considered rituximab refractory (monotherapy part). Efficacy data are also shown, in a side-by-side manor, with data from an earlier assessed ibrutinib monotherapy study, 1118E.

The study design was developed considering the scientific advice from regulatory agencies, including CHMP in 2014. PFS was considered an acceptable endpoint according to this advice. Due to the fact that no single substance, including rituximab, was approved for the treatment of WM, the comparator was discussed. Given the lack of truly evidenced-based therapy, rituximab was considered acceptable by CHMP as comparator and backbone therapy, acknowledging that the reference therapy would be a non-licenced comparator. However CIT (rituximab +chemotherapy) was also considered acceptable. It was suggested that subjects progressing on placebo-rituximab treatment would be able to switch to ibrutinib, given the previous approval. Furthermore, the importance of PFS2 was emphasised because of the unequal duration of treatment between arms.

In the present study (the randomised part) 54.7% of the patients had received previous treatment for WM. Subjects in the untreated cohort (n=68, 45.3%) had received no prior WM therapy; subjects in the previously treated cohort (n=82, 54.7%) had received a median of 2 prior WM therapies.

The majority of recommended therapies for WM are anti-CD-based (rituximab-based) combinations with chemotherapeutic agents or a proteasome inhibitor. The use of rituximab monotherapy, although included in European guidelines among other treatment options for relapsed patients, is associated with lower response rates compared to combination regiments and short duration of response and actually recommended only for patients with comorbidities precluding the use of more effective chemo-immunotherapies. In a recent large retrospective chart review (Lancet Haematol 2018, C Buske et

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al) only 6% of patients received Rituximab monotherapy as first line and second line therapy. In third line setting, monotherapy rituximab was administered in 11% of the patients.

The MAH presented data on the use of monotherapy treatments, including rituximab, at the time of study design and further emphasized the wide heterogeneity in the choice of treatments and also the absence of standard of care. Rituximab was one of the most commonly used monotherapy regimens and a relatively non-toxic treatment option that provided adequate clinical responses and was therefore considered to be an appropriate comparator in both the treatment-naïve and previously treated setting. The goal to explore and chemotherapy-free treatment alternative for WM was supported by the WM Consortium Group.

Efficacy evaluation is based on the modified consensus response criteria from the VIth International workshop for WM (NCC2014).

The sample size calculation was based on an assumption of 15 months median PFS in the control arm. The actual observed PFS was considerably longer and hence suggest that the general condition of the population is healthier than expected. The stratification factors were changed twice during the study due to changes in inclusion criteria. None of the changes to stratification factors across protocol amendments affected the balance in the randomization. No subjects were enrolled or randomized under the original protocol. Therefore, this change did not affect the balance in the randomization. Amendment 1 only allowed for inclusion of subjects with previously treated WM. In protocol Amendment 2 (dated 09 February 2015), the second randomization factor was modified to "Number of prior systemic treatment regimens (0, 1-2, vs. ≥3)" and to add subjects with previously untreated WM. The randomization scheme #2 was then generated for the previously untreated subjects. All the previously treated subjects were randomized according to the randomization scheme #1 and all the untreated subjects were randomized according to the randomization scheme #2. The addition of untreated subjects did not affect the balance in the randomization.

The median number of prior treatments in the monotherapy cohort was 4. In Study 1118E; subjects received a median of 2 prior therapies for WM.

In Study 1127 and the open-label monotherapy substudy ~77 % of subjects had a MYD88 L265P mutation. The mutation status in Study 1118E was not available.

The recommended dose regimen for ibrutinib for WM is unchanged (ie, 420 mg administered orally once daily until disease progression or unacceptable toxicity) and based on earlier studies in WM and CLL/SLL.

The median age of the study population was 70.0 years for the Ibr+R arm and 68.0 years for the Pbo+R arm (range, 36 to 89 years) and the monotherapy arm was 67 years (range, 47 to 90 years). Approximately 60% of the patients were above the 65 year cut-off, with older age defining a strong adverse factor in the prognostic score. This median age corresponds rather well to the median age reported for newly diagnosed WM. The majority of the subjects were recruited from the EU (60%) and 12 % and 13 % from the US and Canada, respectively. Considering that the majority of patients recruited in the EU, a discussion on potential differences in the clinical management/therapy of WM between US and the EU region is in place.

First PFS interim analysis was positive and considered by the applicant to be the final analysis.

The protocol deviations are not considered to be of major importance for the interpretation of the study results.

Treatment was initiated in a larger proportion of patients in the control arm (Pbo+R) due to constitutional symptom(38.7% vs 25.3%); Hgb $\leq$ 10 g/dL (100 g/L), (37.3% vs 26.7%); fatigue (65.3 % vs 56 %); symptomatic organomegaly and/or organ tissue infiltration (9.3% vs 2.7%); IgM related immune

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haemolytic anemia/trombocytopenia (5.3% vs 0%); platelet count $\leq$ 100x10^9 (8.0 5 vs 2.7%). More patients in the Ibr+R arm had their treatment initiated, in a larger proportion due to peripheral neuropathy (20% vs 10.7%) and serum IgM >5 g/dL (24% vs 16%). Peripheral neuropathy due to serum monoclonal protein is a, however clinically significant, heterogeneous group of disorders but not always accompanied with other reasons to initiate treatment for WM, hence as reason for initiation of therapy, neuropathy is difficult to assess in the context of efficacy assessments and the study endpoints. In response to RSI, the applicant has confirmed that, although patients had their treatment initiated due to peripheral neuropathy, the subject also had to meet the other criteria including measurable disease defined as serum monoclonal immunoglobulin M (IgM) >0.5 g/dL. For all evaluable patients, efficacy evaluation was based on the modified Consensus Response Criteria from the VIth International Workshop for WM (NCCN 2014), in which IgM is one of the most important factors.

The medium age for diagnosis of WM is 70 years. The demographic characteristics of patients in study 1127 show a median age of 69 years with a median time since diagnosis just above 5 years. The median time since diagnosis in the treatment-naïve patients was 6.5 months and 94.3 months for the previously treated patients. The median age of patients included in the earlier presented study 1118E, the study which efficacy results are compared below, was 63 years.

An imbalance was seen in the subgroup $\geq$ 75 years, 40% and 26.7% in the Ibr+R and the Pbo+R, respectively. A majority, 78.7 % of the patients had an intermediate or high score according to IPSS for WM, which often coincide with a higher grade of disease specific symptoms. However, 50.2% and 42.7% of the patients were in ECOG 0 and 1, respectively. Presently, only medically unfit patients are recommended rituximab monotherapy, as described in ESMO guidelines.

The study population, in the randomised part, consisted of both earlier treated and untreated patients, and 54,6 % and 54,7% of the patients in the Ibr+R and Pbo+R arm, respectively, had received at least 1 (median 2) earlier line of treatment. Data on earlier treatments is provided in the attachments. An anti-CD20 antibody had been given to 87.8% of the previously treated subjects in the Ibr+R arm and 85.5% in the Pbo+R arm. Only 70% of the patients in Pbo+R completed the rituximab treatment (4 + 4 infusions during weeks 1-4 and 17-20) which strikes as an unusually low number (12% withdraw due to adverse event and 5.3% withdrawal by subject). The MAH clarified that 4 subjects withdrew their consent and 3 subjects were taken off treatment based on investigator decision. Among the 9 subjects in the Pbo+R arm who discontinued treatment due to an adverse event as compared with 2 subjects in the Ibr+R arm, 7 subjects discontinued rituximab due to infusion-related reactions, while none of the subjects in the Ibr+R arm discontinued due to an infusion-related reaction.

Treatment was initiated in a larger proportion of patients in the control arm (Pbo+R) due to constitutional symptom(38.7% vs 25.3%); Hgb $\leq$ 10 g/dL (100 g/L), (37.3% vs 26.7%), fatigue (65.3 % vs 56 %), symptomatic organomegaly and/or organ tissue infiltration (9.3% vs 2.7%), IgM related immune haemolytic anemia/trombocytopenia (5.3% vs 0%), platelet count $\leq$ 100x10^9 (8.0 5 vs 2.7%). On the other hand, more patients in the Ibr+R arm had their treatment initiated, in a larger proportion due to peripheral neuropathy (20% vs 10.7%) and serum IgM >5 g/dL (24% vs 16%). Peripheral neuropathy due to serum monoclonal protein is a, however clinically significant, heterogeneous group of disorders but not always accompanied with other reasons to initiate treatment for WM, hence as reason for initiation of therapy, neuropathy is difficult to assess in the context of efficacy assessments and the study endpoints. In response to RSI, the applicant has confirmed that, howsoever patients had their treatment initiated du to peripheral neuropathy, the subject also had to meet the other criteria including measurable disease defined as serum monoclonal immunoglobulin M (IgM) >0.5 g/dL. For all evaluable patients, efficacy evaluation was based on the modified Consensus Response Criteria from the VIth International Workshop for WM (NCCN 2014), in which IgM is one of the most important factors.

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Efficacy data and additional analyses

A pre-specified interim analysis for the randomized study was planned for 50 IRC-confirmed PFS events and the final analysis was planned for 71 PFS events. This report represents an event-driven analysis, with the data extract completed on 17 October 2017. The interim analysis was conducted with 56 PFS events representing 79% of the planned total PFS events.

The primary endpoint, PFS by IRC assessment was based on the modified Consensus Response Criteria from the VIth International Workshop for WM. The primary endpoint is considered appropriate for both the randomised part and the monotherapy arm.

PFS per IRC assessment showed a statistically significant advantage for Ibr+R as compared with Pbo+R: and significantly reduced the risk of progression or death by 80% compared with Pbo+R; (HR = 0.202 [95% CI: 0.107, 0.380], p <0.0001) (Mod2.7.3/Sec2.2.2 and Sec3.2 and Figure 2). The median PFS per IRC assessment was not reached for the Ibr+R arm and was 20.3 months for the Pbo+R arm. The Kaplan-Meier point estimates of the PFS rate per IRC assessment at 30 months were 81.6% (95% CI: 70.5, 88.9) in the Ibr+R arm and 27.5% (95% CI: 12.8, 44.4) in the Pbo+R arm.

The sensitivity analyses support the result in the primary analysis and the treatment effect was consistent across the all of pre-specified subgroups.

PFS data from the 1127 monotherapy substudy is well in line with the result from the randomised part. For study 1118 updated efficacy analysis are lacking, however presented data (median follow-up time of 14.8 months), the median PFS was not reached for either IRC or INV and the 18-month point estimate of the PFS rate per IRC assessment was 79.5%.

The secondary endpoints Response Rate, RR, (PR or better) per IRC and Clinical Response Rate, CRR, (MR or better) per IRC, both showed statistically convincing results. CRR, which is of clinical relevance in WM, was 92.0% for the Ibr+R arm vs. 46.7% for the Pbo+R arm (rate ratio = 2.001 [95% CI: 1.554, 2.576], p < 0.0001). In the 1127 open-label monotherapy substudy, the CRR was 87.1% (95% CI: 70.2, 96.4) per IRC assessment. The consistency, with results per INV, is acceptable. In Study 1118E, the CRR was 82.5% (95% CI: 70.9, 90.9) per IRC.

Furthermore;

- The response rate (PR or better) per IRC assessment was 72.0% for the Ibr+R arm and 71.0% in the open-label monotherapy substudy. In Study 1118E, the response rate per IRC assessment was 61.9%.
- The CRR (MR or better) per IRC assessment was 92.0% for the Ibr+R arm and 87.1% in the open-label monotherapy substudy. In Study 1118E, the CRR was 82.5% per IRC assessment.
- Median TTnT was not reached for the Ibr+R arm or in the open-label monotherapy substudy. In Study 1118E, TTnT was not assessed.
- Subjects with baseline Hgb ≤110 g/L had sustained improvement in Hgb in the Ibr+R arm (95.5% of subjects), in the Pbo+R arm (56 % of subjects) and in the open-label monotherapy study (81.0% of subjects). In Study 1118E, subjects with baseline Hgb ≤110 g/L, 81.6% of subjects had sustained improvement in Hgb during the study.

The 30-month progression free survival rates were 86% versus 33% among patients with the MYD88^{L265P}/CXCR4 ^{WT} genotype, 80% versus 29% among those with the MYD88 ^{L265P} /CXCR4^{WHIM} genotype, and 80% versus 21% among those with the MYD88 ^{WT} /CXCR4 ^{WT} genotype. For subjects with MYD88 ^{L265P} mutation the HR was 0.191(95% CI: 0.091, 0.402) and for subjects without the MYD88 ^{L265P}

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mutation the PFS HRs was 0.214 (95% CI 0.043, 1.076). The PFS HRs were 0.337 (95% CI: 0.120, 0.948) and 0.165 (95% CI: 0.075, 0.363) for the untreated and previously treated subjects, respectively.

Tumor flare is a well-known phenomenon in WM treated with monotherapy rituximab. In the present study this was seen in 46.7% of the subjects in the Pbo+R arm vs 8% in the experimental arm. The definition of tumor flare is a 25% rise in serum Ig-M level compared to baseline. The same rise in IgM level is the definition for PD (supported by two IgM serum immunoglobulin quantitation, 4 weeks apart). At 3 months already approximately 10% of the subjects in the Pbo+R had an event. Details concerning the instructions for the ICR review, to differentiate between IgM flair and true PD, have been presented.

In terms of the DOR, the median DOR per IRC assessment was not reached for the Ibr+R arm (range [months]: 1.87+, 36.37+) and was 21.2 months for the Pbo+R arm. In the 1127 open-label monotherapy substudy, the median DOR per IRC was not reached (range [months]: 2.43, 34.23+) or per INV (range [months]: 3.75+, 36.07+). In Study 1118E, the median DOR was not reached per assessment by IRC (range [months]: 2.79+, 18.79+) or per INV (range [months]:0.03+, 18.79+).

Infusion reactions were recorded for a substantially fewer subjects in the Ibr+R arm compared to the Pbo+R arm, 1.3 % versus 16 % (see also discussion on clinical safety). Thus Ibrutinib sees clearly to be protective against infusion reactions caused by rituximab.

In regard to overall survival, the median OS was not reached for either treatment arm. There were 4 deaths in the Ibr+R arm and 6 deaths in the Pbo+R arm.

With regard to QoL, by week 25, 68.0% of subjects in the Ibr+R arm and 54.7% of subjects in the Pbo+R arm had a ≥ 3 points increase from baseline in the FACIT-Fatigue subscale score: rate ratio = 1.238 (95% CI: 0.955, 1.603), p = 0.1059.

The overall compliance rates for the EQ-5D-5L PRO measures had a ≥ 90% compliance rate at most time points administered. The EQ-5D-5L visual analogue scale scores and utility scores were similar between the treatment arms at baseline and by Week 25, similar proportions of subjects had clinically meaningful improvements in EQ-5D-5L visual analogue scale (45.3% Ibr+R and 46.7% Pbo+R, p = 0.8859), and utility score (34.7% Ibr+R and 32.0% Pbo+R arm, p = 0.6923).

Median time on study was 26.5 months in the randomised part, and a maturation level in the experimental arm of 18.7 % and 56 % in the control arm for the PFS analysis. For the monotherapy substudy arm the median time on study was 34 months. Date of data extraction was 12 Oct 2017. Data on PFS2 or corresponding proxy was requested and addressed in the MAH's response to the LoQ. Other concerns have been addressed in the MAH´s responses and updates of the time-dependent outcomes are expected at the time of final analysis June 2020. Please see the B/R section for discussions on the appropriateness of the comparator and discussion concerning the add-on structure of the experimental arm.

To understand the potential mechanism of resistance, genetic sequencing has been performed using bone marrow specimens of subjects in arms A, B, and C with incidence of progress disease (PD) collected at week 49, week 97, incidence of PD or suspected PD (sPD), and end of treatment (EOT). Assessment of genetic mutation profile by with the primary goal to examine the known ibrutinib resistance associated hotspot mutations in BTK (codon C481) and PLCG2 (codons R665, S707, L845) genes is planned and a comprehensive analysis using all identified somatic mutations will be performed in next phase. To date, 18 samples derived from 9 PD patients in arm C have been analysed.

During the HTA-CHAMP scientific advice 2014, the applicant was recommended to collect PFS2 data. The applicant informed that a meaningful assessment of PFS after initiation of subsequent antineoplastic treatment (PFS2) could not be made, due to a small number of events. However, the final analysis could serve as the basis of an analysis of PFS2. It is estimated that the clinical study report (CSR) for the final

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analysis will be available for submission by the end of June 2020.

2.4.4. Conclusions on the clinical efficacy

A convincing benefit of Ibr+R over that of Pbo+R was demonstrated with respect to the primary endpoint, sensitivity analyses and most of the secondary endpoints.

Together with efficacy data from study 1118, the presented data from the current study 1127, the effect of ibrutinib in WM has been further supported. Data are compelling and of clinical relevance.

The CHMP recommended the MAH that post-approval data on PFS2 or corresponding proxy be provided (expected in June 2020).

2.5. Clinical safety

Introduction

Individual safety data for ibrutinib from Study 1127 and integrated safety data from the seven studies that presently forms the basis of the currently authorized indications for ibrutinib are presented in parallel. The 7 studies forming the basis of the authorized indications in the ibrutinib European Union (EU) Summary of Product Characteristics (SmPC) are:

- Study PCYC-1118E (hereafter referred to as 1118E) for WM;
- Studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA, and PCI-32765CLL3001 (hereafter referred to as Studies 1102, 1112, 1115, and CLL3001) for chronic lymphocytic leukemia (CLL)
- Studies PCYC-1104-CA and PCI-32765MCL3001 (hereafter referred to as Studies 1104 and MCL3001) for mantle cell lymphoma (MCL).

The 981 ibrutinib-treated subjects from these 7 pivotal studies are referred to as the "Current Label Pool".

Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Severity of AEs was graded by the investigator according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.In general, the treatment-emergent period was defined as the period from the date of the first dose of study treatment (ibrutinib/placebo, rituximab) up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent antineoplastic therapy (including crossover ibrutinib), whichever came first.

Treatment-emergent adverse events (TEAEs) are those events that occurred or worsened during the treatment-emergent period or that were related to the study treatment.

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Patient exposure

Randomised part

Figure 8: Key safety populations supporting the present variation for extended indication in WM

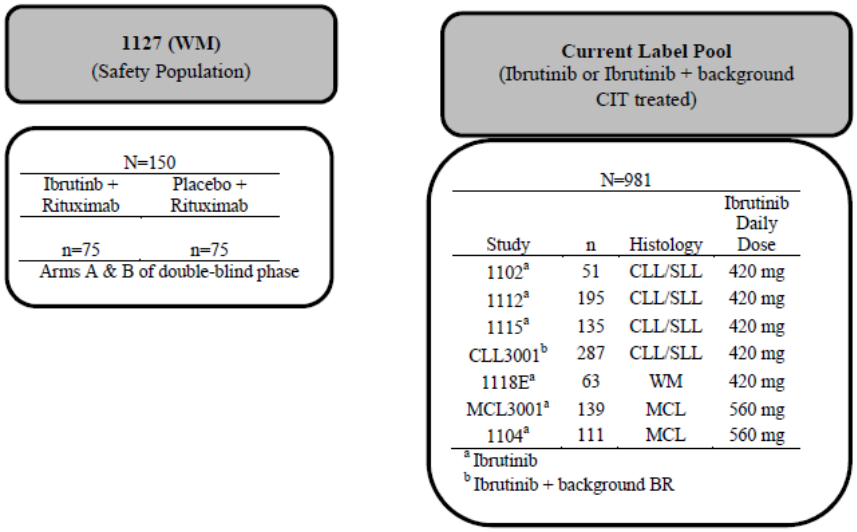


Table 22: Demographic and Base-line characteristics of study population

	PCYC-1127-CA		Current Label Pool
	Ibrutinib+ Rituximab	Placebo+ Rituximab	
Analysis set: Safety Population	75	75	981
Age (years)			
Mean (SD)	69.2 (10.90)	66.1 (11.10)	66.3 (9.73)
Median	70.0	68.0	67.0
Min, Max	(36; 89)	(39; 85)	(30; 89)
< 65 years	28 (37.3%)	30 (40.0%)	371 (37.8%)
≥ 65 years	47 (62.7%)	45 (60.0%)	610 (62.2%)
≥ 70 years	39 (52.0%)	33 (44.0%)	406 (41.4%)
≥ 75 years	30 (40.0%)	20 (26.7%)	201 (20.5%)
Sex			
Male	45 (60.0%)	54 (72.0%)	678 (69.1%)
Female	30 (40.0%)	21 (28.0%)	303 (30.9%)
Race			
White	58 (77.3%)	60 (80.0%)	880 (89.7%)
Black or African American	1 (1.3%)	1 (1.3%)	29 (3.0%)
Asian	3 (4.0%)	0	30 (3.1%)
Other[a]	0	0	12 (1.2%)
Unknown/Not reported	13 (17.3%)	14 (18.7%)	30 (3.1%)
Time from initial diagnosis to randomization/first dose (months)			
Mean (SD)	63.3 (60.63)	71.7 (64.31)	74.3 (57.60)
Median	50.4	55.9	61.7
Range	(1; 257)	(1; 247)	(1; 334)
Lines of prior therapy			
0	34 (45.3%)	34 (45.3%)	135 (13.8%)
1-2	34 (45.3%)	36 (48.0%)	498 (50.8%)
≥ 3	7 (9.3%)	5 (6.7%)	348 (35.5%)
N (≥ 1 prior line)	41	41	846

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Mean (SD)	1.8 (0.94)	1.8 (1.06)	2.7 (1.92)
Median	2.0	2.0	2.0
Range	(1; 5)	(1; 6)	(1; 12)
Region			
North America	19 (25.3%)	15 (20.0%)	397 (40.5%)
Europe	45 (60.0%)	49 (65.3%)	515 (52.5%)
ROW	11 (14.7%)	11 (14.7%)	69 (7.0%)
Creatinine clearance (mL/minute)			
≥60 mL/min	60 (80.0%)	66 (88.0%)	720 (73.4%)
<60 - ≥30 mL/min	15 (20.0%)	6 (8.0%)	252 (25.7%)
<30 mL/min	0	1 (1.3%)	7 (0.7%)
Missing	0	2 (2.7%)	2 (0.2%)
Hepatic Function[b]			
Normal	70 (93.3%)	69 (92.0%)	831 (84.7%)
Abnormal	5 (6.7%)	4 (5.3%)	141 (14.4%)
Mild	5 (6.7%)	4 (5.3%)	129 (13.1%)
Moderate	0	0	11 (1.1%)
Severe	0	0	1 (0.1%)
Missing	0	2 (2.7%)	9 (0.9%)

Max=maximum; Min=minimum; SD=standard deviation; ROW=rest of world

Current Label Pool includes ibrutinib-treated subjects from Studies 1112, 1115, CLL3001, 1118E, 1104, and MCL3001, and 51 previously treated subjects with CLL/SLL treated with ibrutinib 420 mg/day in Study 1102. The intended doses were 560 mg/day in Studies 1104 and MCL3001, and 420 mg/day in Studies 1102, 1112, 1115, CLL3001, and 1118E.

[a] Includes racial categories of American Indian/Alaskan native, Native Hawaiian/other Pacific Islander, Other

[b] Using NCI Organ Dysfunction Working Group criteria.

Table 23: Exposure in Study 1127 and current label pool

Table 2: Extent of Exposure – Study PCYC-1127-CA and Current Label Pool (Safety Population)

	PCYC-1127-CA		Current Label Pool
	Ibrutinib+ Rituximab	Placebo+ Rituximab	
Analysis set: Safety Population	75	75	981
Treatment duration (months)			
Mean (SD)	23.9 (7.89)	15.1 (10.18)	12.9 (6.75)
Median	25.8	15.5	13.0
Min, Max	(0.95; 37.22)	(0.43; 34.33)	(0.03; 28.71)
0 - <6 months	4 (5.3%)	20 (26.7%)	173 (17.6%)
6 - <12 months	2 (2.7%)	14 (18.7%)	265 (27.0%)
12 - <18 months	7 (9.3%)	10 (13.3%)	277 (28.2%)
18 - < 24 months	21 (28.0%)	14 (18.7%)	231 (23.5%)
≥ 24 months	41 (54.7%)	17 (22.7%)	35 (3.6%)
Average dose level per administration[a] (mg/day)			
WM			
N	75	75	63
Mean (SD)	395.2 (40.63)	410.7 (23.77)	390.6 (60.68)
Median	411.2	418.3	416.0
Min, Max	(192.2; 420.0)	(242.7; 430.2)	(158.1; 420.0)
Relative dose intensity (%)			
N	75	75	981
Mean (SD)	94.1 (9.67)	97.8 (5.66)	93.8 (11.06)
Median	97.9	99.6	98.7
Min, Max	(45.8; 100.0)	(57.8; 102.4)	(30.3; 102.4)

Max=maximum; Min=minimum; No=number; SD=standard deviation; WM=Waldenström's macroglobulinemia

Current Label Pool includes ibrutinib-treated subjects from Studies 1112, 1115, CLL3001, 1118E, 1104, and MCL3001, and 51 previously treated subjects with CLL/SLL treated with ibrutinib 420 mg/day in Study 1102. The intended doses were 560 mg/day in Studies 1104 and MCL3001, and 420 mg/day in Studies 1102, 1112, 1115, CLL3001, and 1118E.

[a] Average dose level per administration is calculated as the ratio of total dose administered and total treatment duration. Data shown represent only those subjects with a histology of WM.

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Open label substudy:

31 subjects with WM refractory to prior rituximab-based therapy were enrolled in the open-label monotherapy substudy (Arm C) of 1127 and received treatment with ibrutinib monotherapy. The median age was 67.0 years and more subjects were men (64.5%) and the majority of subjects were white (83.9%). The subjects had received a median of 4 (range: 1 to 7) prior WM therapies. The median time from the last prior treatment to first dose of ibrutinib was 6.1 months.

At the time of the primary analysis for Study 1127, the median time on study for subjects in the open-label monotherapy substudy was 34.4 months, and the median duration of ibrutinib monotherapy was 33.1 months. The majority of subjects (n=17, 54.8%) remained on ibrutinib monotherapy at the time of primary analysis. The most common reason for discontinuation of ibrutinib monotherapy was disease progression.

Adverse events

Randomised part

Table 24: Overall summary of Treatment-emergent Adverse Events (Study 1127 and Current label Pool; safety population)

	PCYC-1127-CA		Current Label Pool
	Ibrutinib+ Rituximab	Placebo+ Rituximab	
Analysis set: Safety Population	75	75	981
Any TEAE	75 (100.0%)	75 (100.0%)	968 (98.7%)
Grade ≥3	45 (60.0%)	46 (61.3%)	687 (70.0%)
Any ibrutinib/placebo-related TEAE	62 (82.7%)	40 (53.3%)	820 (83.6%)
Grade ≥3	29 (38.7%)	11 (14.7%)	430 (43.8%)
Any serious TEAE	32 (42.7%)	25 (33.3%)	466 (47.5%)
Grade ≥3	29 (38.7%)	22 (29.3%)	412 (42.0%)
Drug-related	16 (21.3%)	7 (9.3%)	212 (21.6%)
TEAE leading to discontinuation of ibrutinib or placebo	4 (5.3%)	5 (6.7%)	112 (11.4%)
TEAE leading to ibrutinib or placebo dose reduction	14 (18.7%)	0	81 (8.3%)
TEAE with outcome of death	0	3 (4.0%)	69 (7.0%)

TEAE=treatment-emergent adverse event

Current Label Pool includes ibrutinib-treated subjects from Studies 1112, 1115, CLL3001, 1118E, 1104, and MCL3001, and 51 previously treated subjects with CLL/SLL treated with ibrutinib 420 mg/day in Study 1102. The intended doses were 560 mg/day in Studies 1104 and MCL3001, and 420 mg/day in Studies 1102, 1112, 1115, CLL3001, and 1118E.

Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 20.1.

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Table 25: Incidence of Treatment-emergent Adverse events occuring in 10% or more subjects (by toxicity grade, System Organ Class and Preferred term (Study 1127 and Current label Pool; safety population)

	PCYC-1127-CA		Current Label Pool
	Ibrutinib+ Rituximab	Placebo+ Rituximab	
Analysis Set: Safety Population	75	75	981
Subjects with Any TEAE	75 (100%)	75 (100%)	968 (98.7%)
System Organ Class/ Preferred Term			
Gastrointestinal disorders	44 (58.7%)	31 (41.3%)	707 (72.1%)
Diarrhoea	21 (28.0%)	11 (14.7%)	400 (40.8%)
Nausea	16 (21.3%)	9 (12.0%)	264 (26.9%)
Constipation	10 (13.3%)	8 (10.7%)	160 (16.3%)
Vomiting	2 (2.7%)	8 (10.7%)	141 (14.4%)
Abdominal pain	3 (4.0%)	3 (4.0%)	104 (10.6%)
Dyspepsia	12 (16.0%)	1 (1.3%)	82 (8.4%)
Infections and infestations	52 (69.3%)	31 (41.3%)	700 (71.4%)
Upper respiratory tract infection	6 (8.0%)	3 (4.0%)	184 (18.8%)
Pneumonia	8 (10.7%)	4 (5.3%)	115 (11.7%)
Urinary tract infection	10 (13.3%)	0	89 (9.1%)
Nasopharyngitis	9 (12.0%)	6 (8.0%)	72 (7.3%)
Bronchitis	9 (12.0%)	5 (6.7%)	68 (6.9%)
Influenza	9 (12.0%)	5 (6.7%)	26 (2.7%)
General disorders and administration site conditions	42 (56.0%)	48 (64.0%)	569 (58.0%)
Fatigue	10 (13.3%)	20 (26.7%)	264 (26.9%)
Pyrexia	10 (13.3%)	12 (16.0%)	199 (20.3%)
Oedema peripheral	13 (17.3%)	9 (12.0%)	142 (14.5%)
Asthenia	12 (16.0%)	19 (25.3%)	73 (7.4%)
Blood and lymphatic system disorders	34 (45.3%)	33 (44.0%)	522 (53.2%)
Neutropenia	10 (13.3%)	7 (9.3%)	295 (30.1%)
Thrombocytopenia	4 (5.3%)	8 (10.7%)	195 (19.9%)
Anaemia	14 (18.7%)	22 (29.3%)	191 (19.5%)
Skin and subcutaneous tissue disorders	39 (52.0%)	15 (20.0%)	511 (52.1%)
Rash	2 (2.7%)	0	118 (12.0%)
Ecchymosis	8 (10.7%)	0	33 (3.4%)
Respiratory, thoracic and mediastinal disorders	29 (38.7%)	33 (44.0%)	473 (48.2%)
Cough	13 (17.3%)	8 (10.7%)	192 (19.6%)
Dyspnoea	7 (9.3%)	10 (13.3%)	105 (10.7%)
Musculoskeletal and connective tissue disorders	40 (53.3%)	30 (40.0%)	460 (46.9%)
Muscle spasms	13 (17.3%)	9 (12.0%)	138 (14.1%)
Arthralgia	18 (24.0%)	8 (10.7%)	122 (12.4%)
Back pain	8 (10.7%)	6 (8.0%)	105 (10.7%)
Pain in extremity	9 (12.0%)	5 (6.7%)	69 (7.0%)
Nervous system disorders	30 (40.0%)	30 (40.0%)	344 (35.1%)
Headache	10 (13.3%)	17 (22.7%)	126 (12.8%)
Dizziness	8 (10.7%)	5 (6.7%)	87 (8.9%)
Metabolism and nutrition disorders	26 (34.7%)	17 (22.7%)	342 (34.9%)
Decreased appetite	1 (1.3%)	7 (9.3%)	121 (12.3%)
Hypokalaemia	8 (10.7%)	1 (1.3%)	68 (6.9%)

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Injury, poisoning and procedural complications	44 (58.7%)	50 (66.7%)	286 (29.2%)
Contusion	6 (8.0%)	1 (1.3%)	103 (10.5%)
Infusion related reaction	32 (42.7%)	44 (58.7%)	48 (4.9%)
Vascular disorders	19 (25.3%)	12 (16.0%)	191 (19.5%)
Hypertension	14 (18.7%)	4 (5.3%)	89 (9.1%)
Psychiatric disorders	11 (14.7%)	6 (8.0%)	170 (17.3%)
Insomnia	8 (10.7%)	3 (4.0%)	66 (6.7%)
Cardiac disorders	20 (26.7%)	12 (16.0%)	161 (16.4%)
Atrial fibrillation	11 (14.7%)	2 (2.7%)	63 (6.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (18.7%)	36 (48.0%)	116 (11.8%)
Tumour flare	6 (8.0%)	35 (46.7%)	1 (0.1%)

TEAE=Treatment-emergent adverse event
Current Label Pool includes ibrutinib-treated subjects from Studies 1112, 1115, CLL3001, 1118E, 1104, and MCL3001, and 51 previously treated subjects with CLL/SLL treated with ibrutinib 420 mg/day in Study 1102. The intended doses were 560 mg/day in Studies 1104 and MCL3001, and 420 mg/day in Studies 1102, 1112, 1115, CLL3001, and 1118E.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 20.1.

Modified from: Mod5.3.5.3/ISS/AttTSFAE03A2

Open label sub-study:

TEAEs occurred in 96.8% of subjects, with the most common events (≥20% of subjects) being diarrhea (41.9%), neutropenia (29.0%), back pain (25.8%), hypertension, increased tendency to bruise, nausea, pyrexia, and thrombocytopenia (22.6% each). These events were generally Grade 1-2 in severity.

No fatal TEAEs were reported.

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Table 26: Grade 3 or higher Treatment-emergent adverse events in 5% or more subjects (by toxicity grade, System Organ Class and Preferred term (Study 1127 and Current label Pool; safety population)

	PCYC-1127-CA				Current Label Pool	
	Ibrutinib+Rituximab		Placebo+Rituximab			
	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Analysis Set: Safety Population	75		75		981	
Subjects with Any TEAE	45 (60.0%)	0	43 (57.3%)	3 (4.0%)	618 (63.0%)	69 (7.0%)
System Organ Class						
Preferred Term						
Infections and infestations	17 (22.7%)	0	6 (8.0%)	0	216 (22.0%)	21 (2.1%)
Pneumonia	7 (9.3%)	0	2 (2.7%)	0	71 (7.2%)	4 (0.4%)
Blood and lymphatic system disorders	13 (17.3%)	0	17 (22.7%)	0	354 (36.1%)	0
Neutropenia	7 (9.3%)	0	2 (2.7%)	0	254 (25.9%)	0
Thrombocytopenia	0	0	4 (5.3%)	0	95 (9.7%)	0
Anaemia	8 (10.7%)	0	13 (17.3%)	0	51 (5.2%)	0
Febrile neutropenia	0	0	0	0	52 (5.3%)	0
Metabolism and nutrition disorders	7 (9.3%)	0	6 (8.0%)	0	98 (10.0%)	0
Hyponatraemia	4 (5.3%)	0	2 (2.7%)	0	14 (1.4%)	0
Injury, poisoning and procedural complications	4 (5.3%)	0	13 (17.3%)	0	32 (3.3%)	3 (0.3%)
Infusion related reaction	1 (1.3%)	0	12 (16.0%)	0	4 (0.4%)	0
Vascular disorders	10 (13.3%)	0	6 (8.0%)	0	47 (4.8%)	1 (0.1%)
Hypertension	10 (13.3%)	0	3 (4.0%)	0	33 (3.4%)	0
Cardiac disorders	12 (16.0%)	0	4 (5.3%)	0	61 (6.2%)	5 (0.5%)
Atrial fibrillation	9 (12.0%)	0	1 (1.3%)	0	32 (3.3%)	0

TEAE=treatment-emergent adverse event
Current Label Pool includes ibrutinib-treated subjects from Studies 1112, 1115, CLL3001, 1118E, 1104, and MCL3001, and 51 previously treated subjects with CLL/SLL treated with ibrutinib 420 mg/day in Study 1102. The intended doses were 560 mg/day in Studies 1104 and MCL3001, and 420 mg/day in Studies 1102, 1112, 1115, CLL3001, and 1118E.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was not listed separately Adverse events were coded using MedDRA version 20.1.

Modified from: Mod5.3.5.3/ISS/AttTSFAE02AA2

The overall incidence of Grade 3 or 4 TEAEs in the Ibr+R arm (60%) was consistent with that for the Current Label Pool (63.0%).

Open label sub-study:

Grade 3 or 4 TEAEs were reported in 74.2% of subjects. The most common Grade 3 or 4 TEAEs (≥5% of subjects) were neutropenia (n=5 [16.1%]), hypertension (n=3 [9.7%]), anemia, diarrhea, fatigue, and thrombocytopenia (n=2 subjects each [6.5%]).

Treatment-emergent adverse events over time

Common TEAEs over time (i.e. ≥10% per period) in the randomised part were studied during drug exposure periods of 1 to 90 days, 91 to 180 days, 181 to 270 days and 271 to 365 days.

In the Ibr+R arm of Study 1127, the number of subjects at risk was relatively stable across the time intervals evaluated (from N=75 for Days 1-90 to N=70 for Days 271-365 and N=69 for ≥Days 366), median exposure time of approximately 2 years (25.8 months). For several MedDRA SOCs and common PTs, there was no suggestion of an increase in prevalence with continued ibrutinib. However, for the following common TEAEs (i.e. reported with overall frequency of at least 10%), there was a suggestion of an increase in prevalence with continued ibrutinib treatment (i.e. difference of at least 2-fold) between Days 1-90 and Days 271-365 with consistently higher or stable rates for each subsequent time period: pneumonia (1.3% for Days 1-90; 3.4% for Days 271-365), fatigue (4.5% for Days 1-90; 10.2% for Days 271-365), pyrexia (3.0% for Days 1-90; 6.8% for Days 271-365), and hypertension (4.5% for Days 1-90; 11.9% for Days 271-365).

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Arm C, Pbo+R, shows that, consistent with higher discontinuation rate and a median treatment exposure of 15.5 months reported, the number of subjects at risk declined over time (N=75 for Days 1-90, N=47 for Days 271-365 and N=42 for ≥Days 366).

Similarly, the number of subjects at risk for the Current Label Pool declined over time on ibrutinib therapy, from N=981 for Days 1-90 to N=713 for Days 271-365 and N=560 for ≥Days 366), consistent with the median treatment exposure of 13 months.

The decline in the number of subjects at risk over time limits interpretation of prevalence rates across the specified intervals. In general, however, there were no apparent trends of an increase in prevalence over time for any specific common TEAEs in the Current Label Pool, with the exception of hypertension which was reported at prevalence rates of 3.4% for Days 1-90 and 7.9% for Days 271-365.

Adverse Events of Special Interest

Certain events of potential clinical relevance, included in the EU RMP, were selected based on clinical importance, frequency of occurrence, or preclinical observations. A summary of these events in study 1127 follows below.

Hemorrhagic events

Bleeding TEAEs occurred in 50.7% (4.0% Grade 3-4) in the Ibr+R arm, whereof the most common vas ecchymosis (10.7%), Epistaxis, increased tendency to bruise, petechiae (9.3% each), contusion (8.0%), and traumatic hematoma (5.3%); all were Grade 1 or 2. Major hemorrhagic TEAEs occurred in 3 subjects (4.0%): hemoptysis, melena, and purpura (1 subject each); none were fatal.

Current label pool: Bleeding events 41.4% (3,2% grade 3-4), ecchymosis 3,4%, Epistaxis 8.3, increased tendency to bruise 4.2, petechiae 6,8. Contusion 10.5 traumatic hematoma1,5. 2 fatalities (0,3%)

In the Pbo+R arm bleeding TEAEs occurred in 21.3% of subjects whereof the most common event was epistaxis (8.0%); most were Grade 1 or 2. One hemorrhagic TEAE led to placebo discontinuation: immune thrombocytopenic purpura (1 subject) (Attachment 3-Table 14.3.1.8.1). Major hemorrhagic TEAEs occurred in 3 subjects (4.0%): epistaxis in 1 subject, hematuria in the second subject, and gastrointestinal hemorrhage, hemorrhage intracranial (Grade 5), and immune thrombocytopenic purpura in the third subject.

Approximately 40% all subjects in the Ibr+R (41.3%) or Pbo+R (36.0%) arms in Study 1127, and 49.5% of subjects in the Current Label Pool, used concomitant anticoagulant and/or antiplatelet medication at any time during the study treatment period.

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Table 27: Treatment-emergent Major Hemorrhagic Adverse Events

	Ibr+R (N=75) n (%)			Pbo+R (N=75) n (%)		
MedDRA Preferred Term	**Any Grade**	**Grade 3+4**	**Grade 5**	**Any Grade**	**Grade 3+4**	**Grade 5**
Subjects with any TEAE	**3 (4.0)**	**3 (4.0)**	**0**	**3 (4.0)**	**2 (2.7)**	**1 (1.3)**
Haemoptysis	1 (1.3)	1 (1.3)	0	0	0	0
Melaena	1 (1.3)	1 (1.3)	0	0	0	0
Purpura	1 (1.3)	1 (1.3)	0	0	0	0
Epistaxis	0	0	0	1 (1.3)	1 (1.3)	0
Gastrointestinal haemorrhage	0	0	0	1 (1.3)	1 (1.3)	0
Haematuria	0	0	0	1 (1.3)	1 (1.3)	0
Haemorrhage intracranial	0	0	0	1 (1.3)	0	1 (1.3)
Immune thrombocytopenic purpura	0	0	0	1 (1.3)	1 (1.3)	0

CNS: central nervous system; Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab; SMQ: Standardized MedDRA Query; TEAE: treatment-emergent adverse event.

Subjects with multiple events for a given preferred term are counted once only using maximum severity for each preferred term.

Events are sorted by decreasing frequency of preferred term by Any Grade column in the Ibr+R group.

Major hemorrhage includes serious or Grade ≥3 hemorrhage and CNS hemorrhage at any grade among bleeding events identified by haemorrhage SMQ excluding laboratory terms.

Adverse events are coded by MedDRA Version 20.0.

Source: Attachment 3-Table 14.3.1.12.2

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Leucostasis

Yhere were no TEAEs reported in any of the treatment arms in study 1127. (Current label pool: 1 subject).

Tumor Lysis Syndrome (TLS)

No TEAEs of TLS occurred in ether of the study arms. (Current label pool: 12 subjects =1.2%, majority seen in CLL).

Cytopenic Adverse Events

Table 28: Sumamry of TEAEs ; cytopenia

Table 10: Summary of Treatment-emergent Cytopenia Adverse Events - Study PCYC-1127-CA and Current Label Pool (Safety Population)

	PCYC-1127-CA		Current Label Pool
	Ibrutinib + Rituximab	Placebo + Rituximab	
Analysis set: Safety Population	75	75	981
Neutropenia			
Any grade	10 (13.3%)	7 (9.3%)	295 (30.1%)
Grade 3 or 4	7 (9.3%)	2 (2.7%)	254 (25.9%)
Serious TEAE	0	0	12 (1.2%)
TEAE leading to treatment discontinuation	0	0	5 (0.5%)
TEAE leading to dose reduction	3 (4.0%)	0	17 (1.7%)
Febrile neutropenia	0		
Any grade	1 (1.3%)	0	52 (5.3%)
Grade 3 or 4	0	0	52 (5.3%)
Serious TEAE	0	0	40 (4.1%)
TEAE leading to treatment discontinuation	0	0	1 (0.1%)
TEAE leading to dose reduction	0	0	3 (0.3%)
Anemia			
Any grade	14 (18.7%)	22 (29.3%)	191 (19.5%)
Grade 3 or 4	8 (10.7%)	13 (17.3%)	51 (5.2%)
Serious TEAE	2 (2.7%)	0	12 (1.2%)
TEAE leading to treatment discontinuation	0	0	1 (0.1%)
TEAE leading to dose reduction	0	0	1 (0.1%)
Thrombocytopenia			
Any grade	4 (5.3%)	8 (10.7%)	195 (19.9%)
Grade 3 or 4	0	4 (5.3%)	95 (9.7%)
Serious TEAE	0	0	12 (1.2%)
TEAE leading to treatment discontinuation	0	0	6 (0.6%)
TEAE leading to dose reduction	0	0	6 (0.6%)

TEAE=treatment-emergent adverse event

Current Label Pool includes ibrutinib-treated subjects from Studies 1112, 1115, CLL3001, 1118E, 1104, and MCL3001, and 51 previously treated subjects with CLL/SLL treated with ibrutinib 420 mg/day in Study 1102. The intended doses were 560 mg/day in Studies 1104 and MCL3001, and 420 mg/day in Studies 1102, 1112, 1115, CLL3001, and 1118E.

Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 20.1.

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Infections

Table 29: Summary of TEAEs; Infections

System Organ Class MedDRA Preferred Term	Ibr+R (N=75) Any Grade n(%)	Ibr+R (N=75) Grade 3+4 n(%)	Ibr+R (N=75) Grade 5 n(%)	Pbo+R (N=75) Any Grade n(%)	Pbo+R (N=75) Grade 3+4 n(%)	Pbo+R (N=75) Grade 5 n(%)
Infections And Infestations	52 (69.3)	17 (22.7)	0	31 (41.3)	6 (8.0)	0
Urinary Tract Infection	10 (13.3)	0	0	0	0	0
Bronchitis	9 (12.0)	2 (2.7)	0	5 (6.7)	0	0
Influenza	9 (12.0)	0	0	5 (6.7)	1 (1.3)	0
Pneumonia	8 (10.7)	7 (9.3)	0	4 (5.3)	2 (2.7)	0
Viral Upper Respiratory Tract Infection	8 (10.7)	0	0	5 (6.7)	0	0
Upper Respiratory Tract Infection	6 (8.0)	1 (1.3)	0	3 (4.0)	0	0
Gastroenteritis	5 (6.7)	2 (2.7)	0	1 (1.3)	0	0
Herpes Zoster	5 (6.7)	0	0	1 (1.3)	0	0
Respiratory Tract Infection	5 (6.7)	2 (2.7)	0	2 (2.7)	0	0
Oral Herpes	4 (5.3)	0	0	0	0	0
Rhinitis	4 (5.3)	0	0	1 (1.3)	0	0

Subjects with multiple events for a given preferred term or system organ class are counted once only using maximum severity under each preferred term or system organ class, respectively.
Events are sorted by system organ class alphabetically and decreasing frequency of preferred term by Any Grade column in the ibrutinib+R group.
Adverse events are coded by MedDRA Version 20.0. [*]: Unknown Cause of Death.

In Study 1127, pneumonia-related TEAEs was reported for 18.7% of subjects in theIbr+R arm (13.3% Grade 3 or 4). For the majority of subjects in the Ibr+R arm with a pneumonia-related TEAE, the event was serious. No reported pneumonia-related TEAE resulted in a reduction in dose or discontinuation of ibrutinib in Study 1127.

Severe gastrointestinal disorders

In Study 1127, severe GI TEAEs (Grade 3 or 4) were reported for 2 subjects (2.7%) in the Ibr+R (one report each of Grade 3 or 4; constipation and vomiting). Neither of the Grade 3 or 4 GI TEAEs resulted in a reduction in the dose of ibrutinib or discontinuation of ibrutinib treatment The Grade 3 or 4 TEAE of constipation was serious.

Two subjects (2.7%) in the Pbo+R arm of Study 1127 had a severe GI TEAE (one report each of Grade 3 or 4 diarrhea and constipation). Both of these events were serious.

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Other Malignancies, Including Non-melanoma Skin Cancer

Table 30: Summary of secondary malignancies

Subcategory Preferred Term	Ibr+R (N=75) n (%)			Pbo+R (N=75) n (%)		
	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5
Non-melanoma skin cancer	4 (5.3)	0	0	4 (5.3)	1 (1.3)	0
Basal cell carcinoma	2 (2.7)	0	0	2 (2.7)	1 (1.3)	0
Atypical fibroxanthoma	1 (1.3)	0	0	0	0	0
Keratoacanthoma	1 (1.3)	0	0	0	0	0
Squamous cell carcinoma	0	0	0	3 (4.0)	0	0
Melanoma skin cancer	1 (1.3)	0	0	0	0	0
Malignant melanoma	1 (1.3)	0	0	0	0	0
Non-skin cancer	2 (2.7)	0	0	0	0	0
Breast cancer	1 (1.3)	0	0	0	0	0
Prostate cancer	1 (1.3)	0	0	0	0	0

Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab.
Subjects with multiple events for a given preferred term are counted once only using maximum severity for each preferred term.
Events are sorted by decreasing frequency of preferred term in the Ibr+R group under each subcategory.
Adverse events are coded by MedDRA Version 20.0.

TSFAE24A2: Incidence of Other Malignancy Adverse Events by Preferred Term - PCYC-1127-CA and Current Label Pool; Safety Population			
	Ibrutinib+R	Placebo+R	Current Label Pool
Analysis Set: Safety Population	75	75	981
Subjects with Any Other Malignancy	5 (6.7%)	4 (5.3%)	83 (8.5%)

Non-skin cancer TEAEs were reported for 2 subjects (2.7%) in the Ibr+R arm (none in Pbo+R) arm) of Study 1127 and consisted of 1 report each of prostate cancer and breast cancer. In the Current Label Pool, non-skin cancer TEAEs occurred in 2.5% of ibrutinib-treated subjects, with most of these representing single occurrences of a particular cancer type.

Hypertension

In the Ibr+R arm, hypertension TEAEs occurred in 18.7.0% of subjects (13.3% Grade 3 or 4). For 1 subject in this treatment arm (1.3%), the hypertension TEAE was serious (Grade 3 or 4); no subject had the dose of ibrutinib reduced or discontinued as a result of a hypertension TEAE.

In the Pbo+R arm, hypertension TEAEs occurred in 5.3% of subjects (4.0% Grade 3 or 4).

The reported incidence of hypertension TEAEs in the Ibr+R arm was higher, compared to the Current Label Pool (9.9%, with Grade 3 or 4 events 3.8%).

Few subjects in the Current Label Pool had a hypertension TEAE that was serious (0.6%; all Grade 3 or 4) or resulted in ibrutinib dose reduction (0.1%) or ibrutinib discontinuation (0.1%)

Cardiac Arrhythmias

- Atrial fibrillation

In Study 1127, atrial fibrillation TEAEs occurred in 11 (14.7%) subjects in the Ibr+R arm, and 2 subjects (2.7%) in the Pbo+R arm. The majority of the events were manageable without treatment discontinuation and 8 of the 14 events were reported as resolved. Three of the 11 subjects in the Ibr+R arm with atrial fibrillation discontinued the study drug and led to a reduction of the ibrutinib dose. In 1 subject in the Pbo+R arm the event was serious, and Grade 3 or 4 in severity.

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Table 31: Other Cardiac Arrhythmias (excluding atrial fibrillation)

TSFAE35A2: Incidence of Treatment-emergent Cardiac Arrhythmias (Excluding Atrial Fibrillation) Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - PCYC-1127-CA and Current Label Pool; Safety Population

	Ibrutinib+R			Placebo+R			Current Label Pool		
	All Grades	Grade 3-4	Grade 5	All Grades	Grade 3-4	Grade 5	All Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	75			75			981		
Subjects with Any Treatment-emergent Cardiac Arrhythmias	8 (10.7%)	1 (1.3%)	0	7 (9.3%)	1 (1.3%)	0	99 (10.1%)	18 (1.8%)	5 (0.5%)
System Organ Class									
Preferred Term									
Cardiac disorders	7 (9.3%)	0	0	6 (8.0%)	0	0	80 (8.2%)	10 (1.0%)	4 (0.4%)
Palpitations	3 (4.0%)	0	0	0	0	0	22 (2.2%)	0	0
Sinus tachycardia	0	0	0	1 (1.3%)	0	0	12 (1.2%)	0	0
Tachycardia	0	0	0	1 (1.3%)	0	0	9 (0.9%)	0	0
Sinus bradycardia	1 (1.3%)	0	0	0	0	0	7 (0.7%)	0	0
Atrial flutter	0	0	0	0	0	0	6 (0.6%)	2 (0.2%)	0
Supraventricular tachycardia	0	0	0	0	0	0	5 (0.5%)	1 (0.1%)	0
Bradycardia	1 (1.3%)	0	0	0	0	0	4 (0.4%)	0	0
Cardiac arrest	0	0	0	0	0	0	4 (0.4%)	1 (0.1%)	3 (0.3%)
Ventricular extrasystoles	1 (1.3%)	0	0	0	0	0	4 (0.4%)	0	0
Atrioventricular block	0	0	0	0	0	0	3 (0.3%)	2 (0.2%)	0
Atrial tachycardia	1 (1.3%)	0	0	0	0	0	2 (0.2%)	0	0
Atrioventricular block second degree	0	0	0	0	0	0	2 (0.2%)	0	0
Extrasystoles	0	0	0	1 (1.3%)	0	0	2 (0.2%)	0	0
Ventricular arrhythmia	0	0	0	1 (1.3%)	0	0	2 (0.2%)	0	0
Ventricular tachycardia	0	0	0	1 (1.3%)	0	0	2 (0.2%)	1 (0.1%)	0

Serious adverse events, deaths and other significant adverse events

Serious adverse events

Serious adverse events occurred in the Ibr+R arm in 42.7% of subjects (≥ 5% of subjects), whereof the most common events were pneumonia (8.0%), and atrial fibrillation (6.7%).

In the Pbo+R arm, serious TEAEs occurred in 33.3% of subjects; the most common events (≥ 5% of subjects) were infusion related reaction (6.7%).

One subject in the Pbo+R arm had a NMSC TEAE (squamous cell carcinoma).

Table 32Treatment-emergent serious adverse events with subject incidence >2% in either arm (randomised study)

	Ibr+R (N=75) n (%)			Pbo+R (N=75) n (%)		
MedDRA Preferred Term	**Any Grade**	**Grade 3+4**	**Grade 5**	**Any Grade**	**Grade 3+4**	**Grade 5**
Subjects with any TEAE	**32 (42.7)**	**29 (38.7)**	**0**	**25 (33.3)**	**19 (25.3)**	**3 (4.0)**
Pneumonia	6 (8.0)	6 (8.0)	0	2 (2.7)	2 (2.7)	0
Atrial fibrillation	5 (6.7)	5 (6.7)	0	1 (1.3)	1 (1.3)	0
Respiratory tract infection	3 (4.0)	2 (2.7)	0	0	0	0
Anaemia	2 (2.7)	2 (2.7)	0	0	0	0
Arthralgia	2 (2.7)	2 (2.7)	0	0	0	0
Cardiac failure congestive	2 (2.7)	2 (2.7)	0	0	0	0
Fall	2 (2.7)	2 (2.7)	0	0	0	0
Gastroenteritis	2 (2.7)	2 (2.7)	0	0	0	0
Myocardial ischaemia	2 (2.7)	1 (1.3)	0	0	0	0
Infusion related reaction	0	0	0	5 (6.7)	4 (5.3)	0

Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab; TEAE: treatment-emergent adverse event.

Subjects with multiple events for a given preferred term are counted once only using maximum severity for each preferred term. Events are sorted by decreasing frequency of preferred term by Any Grade column in the Ibr+R group.

Adverse events are coded by MedDRA Version 20.0.

Source: Attachment 3-Table 14.3.1.10.2

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Deaths

In the Ibr+R arm, no fatal TEAEs occurred. There were 3 Grade 5 TEAE (death), all in the Pbo+R arm in the randomised part of the study (unknown cause, hemorrhage intracranial, and nervous system disorder).

Adverse Events Leading to Treatment Discontinuation

TEAEs leading to ibrutinib discontinuation in the Ibr+R arm were reported for 4 subjects (5.3%): atrial fibrillation (3 subjects), interstitial lung disease, and rash macular (1 subject each).

Rituximab discontinuation was reported for 2 subjects (atrial defibrillation and variant angina, 1 subject each).

In the Pbo+R arm, TEAEs leading to placebo discontinuation were reported for 5 subjects, 6.7% (asthenia, 2 subjects and Brugada syndrome, immune thrombocytopenic purpura, and night sweats, 1 subject each).

TEAEs leading to rituximab discontinuation were reported for 9 subjects, 12.0% (infusion related reaction,7 subjects and asthenia and Brugada syndrome (1 subject each).

No subjects had TEAE of tumor lysis syndrome or leucostasis, in either arm. Neither was any TLS or leucostasis seen in the monotherapy substudy.

Adverse Events Leading to Dose Reduction

Ibrutinib dose reduction was reported for 14 subjects (18.7%) in the Ibr+R arm. Events leading to dose reduction for two or more subjects were neutropenia (n=3) and atrial fibrillation (n=2) and muscle spasm (n=2). There were no dose reductions of placebo in the Pbo+R arm.

Table 33 Adverse Events Leading to Death

MedDRA Preferred Term	Ibr+R (N=75) n (%)	Pbo+R (N=75) n (%)
Subjects with any fatal TEAE	**0**	**3 (4.0)**
Death[a]	0	1 (1.3)
Haemorrhage intracranial	0	1 (1.3)
Nervous system disorder[b]	0	1 (1.3)

Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab; TEAE: treatment-emergent adverse event.
Subjects with multiple events for a given preferred term are counted once only for each preferred term.
Adverse events are coded by MedDRA Version 20.0.
Events are sorted by decreasing frequency of preferred term in the Ibr+R group.
[a] Unknown cause of death.
[b] Bing-Neel syndrome (Appendix 23, Subject 1127-0581-009).
Source: Attachment 3-Table 14.3.1.11

Open label sub-study:

Serious TEAEs were reported in 35.5% of subjects; no individual serious TEAE preferred term was reported in more than 1 subject each.

In the open-label monotherapy substudy, no subject had a major hemorrhagic TEAE, or TEAEs of TLS, leukostasis syndrome, atrial fibrillation, ILD, or SCAR. One subject (3.2%) had a NMSC TEAE (squamous cell carcinoma), and 1 subject had a non-skin cancer TEAE (renal cell carcinoma).

No fatal TEAEs occurred during the monotherapy ibrutinib treatment.

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Hypertension TEAEs were reported in 8 (25.8%) subjects and cardiac arrhythmias (excluding atrial fibrillation) were reported in 4 subjects. There were no cases of atrial fibrillation.

Infection TEAEs were reported in 22 (71.0%) subjects; for 6 (19.4%) subjects, the infection TEAE was Grade 3 or 4 in severity. One subject had an Aspergillus infection (Grade 3 or 4).

TEAEs were the reported as the primary reason for ibrutinib discontinuation for 2 subjects (6.5%) and consisted of constipation and diarrhea (reported as reason for discontinuation in 1 subject each).Till discontinuation.

Laboratory findings

In the Ibr+R arm, TEAE Grade 3 or 4 decreases in ANC occurred in 9.3% of subjects, and Grade 3 or 4 decreases in Hgb and platelets occurred in 1.3% of subjects each. In the Pbo+R arm, TEAE Grade 3 or 4 decreases in ANC occurred in 6.7% of subjects, and Grade 3 or 4 decreases in Hgb and platelets occurred in 10.7% and 5.3% of subjects, respectively.

Table 34: Worst post-baseline toxicity grade in chemistry parameters

		Ibr+R (N=75)		Pbo+R (N=75)	
Laboratory Parameter	**Direction of Toxicity**	**Any Grade n (%)**	**Grade 3+4 n (%)**	**Any Grade n (%)**	**Grade 3+4 n (%)**
Alanine Aminotransferase	High	18 (24.0)	1 (1.3)	10 (13.3)	0
Aspartate Aminotransferase	High	10 (13.3)	0	5 (6.7)	0
Alkaline Phosphatase	High	16 (21.3)	0	8 (10.7)	0
Bilirubin	High	13 (17.3)	0	8 (10.7)	1 (1.3)
Corrected calcium	High	2 (2.7)	0	2 (2.7)	0
	Low	7 (9.3)	0	2 (2.7)	1 (1.3)
Creatinine	High	16 (21.3)	0	10 (13.3)	0
Creatinine Clearance	Low	31 (41.3)	2 (2.7)	34 (45.3)	1 (1.3)
Potassium	High	12 (16.0)	1 (1.3)	16 (21.3)	1 (1.3)
	Low	9 (12.0)	1 (1.3)	2 (2.7)	0
Magnesium	High	1 (1.3)	0	0	0
	Low	5 (6.7)	0	1 (1.3)	0
Sodium	High	8 (10.7)	0	3 (4.0)	0
	Low	8 (10.7)	4 (5.3)	4 (5.3)	3 (4.0)

CTCAE: Common Terminology Criteria for Adverse Events; Ibr+R: ibrutinib and rituximab; Pbo+R: placebo and rituximab.
Parameters were graded using CTCAE Version 4.03 with the modification of creatinine, which was graded by CTCAE Version 4.03 criteria for values increased above upper limit of normal range only. Central lab results are used in this summary.
Data up to 30 days after the last dose of study treatment or initiation of subsequent antineoplastic treatment/crossover ibrutinib, whichever occurs earlier, are included.
n: number of subjects who got worsened from baseline.

Vital signs physical findings and other observation related to safety

In the Ibr+R arm Hypertension TEAEs occurred in 20.0% of subjects, the corresponding finding in the Pbo+R arm was 5.3%. No clinically meaningful changes were observed for other vital signs (heart rate, temperature, weight) in either group.

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Safety in special populations

Of the 1,200 patients treated with ibrutinib in the Overall Label Pool, 64% were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently among elderly patients treated with ibrutinib (12% of patients age ≥65 versus 7% of patients <65 years of age).

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Table 35: Treatment withdrawal information (Studies 1127-CA and 1118E)

	Study 1127 (Intent-to-Treat Population)		Single-agent Ibrutinib	
			Study 1127 Open-label Substudy (All-treated Population)	Study 1118E (All-treated Population)
	Ibr+R (N=75) n (%)	Pbo+R (N=75) n (%)	Ibrutinib (N=31) n (%)	Ibrutinib (N=63) n (%)
Subjects discontinued study treatment	19 (25.3)	49 (65.3)	14 (45.2)	12 (19.0)
Subjects discontinued study	6 (8.0)	11 (14.7)	5 (16.1)	8 (12.7)
Time (months) on study[a]				
Median (95% CI)	26.7 (25.9, 27.7)	26.0 (23.8, 27.1)	34.4 (33.9, 35.2)	14.8 (11.1, 15.5)
Min, Max	4.6, 38.9	0.5+, 37.3	8.6+, 37.7	3.5, 21.1

CI=confidence interval; Ibr+R=ibrutinib and rituximab; max=maximum; min=minimum; N (n)=number; Pbo+R=placebo and rituximab.

N: number of subjects in specified population.

[a] Time on study is defined as the interval between randomization date for randomized subjects (or the date of first dose of study drug for subjects in the open-label monotherapy substudy of Study 1127 and Study 1118E) and the date last known alive (the same way as overall survival with reversed censoring).

+ Indicates censored observation.

2.5.1. Discussion on clinical safety

The safety evaluation rests on a total of 981 patients that constitutes the integrated dataset (= current label pool) which includes the 63 WM patients from the pivotal 1118E study. The present variation for extended indication in WM adds further 150 patients to the safety evaluation. A total of 213 patients, given the rarity of WM, are considered acceptable.

Apart from the 1127 study, the integrated dataset consists of study 1118E in WM (WM, n=63) of studies 1102 (CLL/SLL, n=51), 1112 (CLL/SLL, n=195), 1115 (CLL/SLL, n=135) and CLL3001 (CLL/SLL, and n=287). Studies MCL3001 (MCL, n=139) and 1104 (MCL, n=111).This is referred to as the Current Label Pool.

The safety population was defined as all patients who received at least one dose of ibrutinib and it should be noted that the posology differs between indications i.e. MCL (560 mg/daily) versus CLL/SLL and WM (both 420 mg/daily). In addition to the current label pool, safety data from, a presently assessed parallel

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procedure, Study 1130 (CLL/SLL) is incorporated, now comprising 1,200 subjects treated with ibrutinib for CLL, WM, or MCL, constitutes the Overall Label Pool.

The median duration of exposure to ibrutinib in the 1127 study was 26 months (median average dos of 411 mg/day) compared to 13 months in the current label pool (median average dos of 416 mg/day). The study also includes time-truncated data.

All patients in the 1127 study had at least one TEAE. In the Ibr+R arm a high incidence reported for various SOCs (e.g. gastrointestinal disorder; 59%, infections/infestations; 69%, general disorder; 56%, blood and lymphatic system disorder; 45%, skin and subcutaneous tissue disorder; 52%, respiratory, thoracic and mediastinal system disorder; 39%, musculoskeletal and connective tissue disorder; 53%, nervous system disorders; 40%). About 60 % of the patients in the 1127 study reported any Grade 3 or 4 event (both arms).

Frequency of infusion related reactions to rituximab were observed in a considerably lower rate in the Ibr+R arm versus the Pbo+R arm.

In the 1127 study, there were 3 Grade 5 TEAE (death), all in the Pbo+R arm in the randomised part of the study (1 unknown cause, 1 hemorrhage intracranial, and 1 nervous system disorder).

The safety profile of the 1127 study was largely consistent with the current label pool, with the exception of hypertension (13 % vs 3 % in the Ibr+R arm and current label pool, respectively) and atrial fibrillation (12% vs 3 %, Ibr+R arm and current label pool, respectively). The time-truncated data showed an increased prevalence of hypertension, by time of exposure to ibrutinib. This however, was not the case for atrial fibrillation. An increased frequency was also seen for arthralgia which occurred in a more than doubled rate in Ibr+R arm compared to both the Pbo+R arm and the current label pool (24% vs 11% and 12%) and was not reported to be time dependent.

In the Ibr+R arm, no fatal TEAEs occurred, however, but in the Pbo+R arm, fatal TEAEs occurred in 3 subjects (4.0%): death (unknown cause), intracranial haemorrhage, and nervous system disorder. The reported figure from the current label pool was 7 %. In all there were 10 deaths reported (4 vs 6 Ibr+R arm and the Pbo+R arm, respectively.

TEAEs lead to discontinuation of study drug in 5.3 % and 6.7 % in the Ibr+R arm and the Pbo+R arm, respectively. Treatment-emergent AEs leading to rituximab discontinuation were reported for 2 subjects in the Ibr+R arm. The rate of discontinuation of study drug in the current label pool was 11.4 %. Dose reduction was seen in 18.7 % in the Ibr+R arm (mainly neutropenia, atrial fibrillation and muscle spasms). In the current label pool fewer subjects had a dose reduction, 11.4%. No subjects in Pbo+R arm had any dose reduction due to TEAE.

TEAE grade ≥ 3 occurred in 60 % vs 61 % in the Ibr+R arm and the Pbo+R arm, respectively and 70 % in the current label pool. The most common TEAEs grade ≥ 3 were infections and blood and lymphatic disorder. Any serious TEAE grade $\geq$ 3 occurred in 38.7 % and 29.3%, in the Ibr+R arm and the Pbo+R arm, respectively, while this was seen in 42% in the current label pool. One of the TEAEs of clinical interest concerns bleeding; in the Ibr+R arm, TEAEs occurred in 50.7%, the most common events ($\geq$ 5 % of subjects) were ecchymosis (10.7%), epistaxis, increased tendency to bruise, petechiae (9.3% each). Major haemorrhagic TEAEs occurred in 3 subjects (4.0%): hemoptysis, melena, and purpura (1 subject each); none were fatal. The proportion of subjects with a haemorrhage TEAE of any grade/severity or with a major haemorrhagic TEAE in the Ibr+R arm of Study 1127 were consistent with those observed in the Current Label Pool. Bleeding TEAEs in the Pbo+R arm occurred in 21.3% of subjects; the most common event ($\geq$ 5% of subjects) were epistaxis (8.0%); most were Grade 1 or 2.

Infusion reactions was recorded for a substantially fewer subjects in the Ibr+R arm compared to the Pbo+R arm, 1.3 % versus 16 %.

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Infections were among the most common events in the Ibr+R arm, reported in 69.3% of subjects (22.7% Grade 3 or 4). In Study 1127, there were no events of Aspergillus infections in the Ibr+R arm, there was a single case of Aspergillus infection in the open-label substudy of ibrutinib monotherapy. Infection-related TEAEs were reported at a lower rate in the Pbo+R arm (41.3% any grade; 8.0% Grade 3-4; 5.3% serious) than in the Ibr+R arm in Study 1127. In the current label pool, frequencies observed for ibrutinib-treated subjects of infection TEAEs of any grade, Grade 3 or 4, or serious events, was consistent with Ibr+R arm of Study 1127.

The incidence of severe GI TEAEs in the Ibr+R arm was lower than that for the Current Label Pool (8.7% Grade 3 or 4; 0.2% Grade 5) but resulted in ibrutinib discontinuation for only a small minority (n=7, 0.7%). Diarrhea (3.2%) and abdominal pain (2.0%) were the most frequent severe (and serious) GI TEAEs in the Current Label Pool.

The increased prevalence in hypertension observed in Ibr+R might be a consequence from longer time on treatment. However, there was no increase in prevalence over time observed for atrial fibrillation. There was a doubled rate of TEAE atrial fibrillation in the Ibr+R arm (any grade 14.7%, Grade 3 or higher: 13.3%) compared to the current label pool (any grade 6.4%, Gr 3 or higher: 3.4%).

Atrial fibrillation TEAEs in the Current Label Pool generally did not result in dose reduction or discontinuation of ibrutinib treatment (0.1% and 0.7% subjects respectively) and were not serious for the majority of subjects (3.1% of subjects had serious atrial fibrillation).

Similar frequencies of cardiac arrhythmia TEAEs (excluding atrial fibrillation) was reported in both arms of study 1127 (Ibr+R arm: 10.7% and Pbo+R 9.3%). The pattern of cardiac arrhythmia TEAEs in the Ibr+R arm was consistent with that observed for ibrutinib-treated subjects in the Current Label Pool. In the Current Label Pool, the frequency of cardiac arrhythmia TEAEs (excluding atrial fibrillation) of any grade was 10.1%.

One subject experienced a ventricular tachyarrhythmia TEAE in the Ibr+R arm (Grade 1 ventricular extra systoles), this did not result in ibrutinib dose reduction or discontinuation. Two subjects (2.7%) in the Pbo+R arm of Study 1127 had a ventricular tachyarrhythmia TEAE. The occurrence of ventricular tachyarrhythmia TEAEs in subjects in the Ibr+R in Study 1127 was consistent with the pattern of these events in the Current Label Pool, where 1.0% of subjects had a ventricular tachyarrhythmia TEAE, most of which were Grade 1 or 2 in severity.

No change in Other Malignancy frequency or pattern is seen, due to low and constant frequency, in 1127 compared to the current label pool. Treatment-emergent AEs of tumor flare were excluded from the other malignancy summaries, as these events were assessed separately. Tumor flare, associated with the usage of rituximab in WM, and which in WM only counts for a temporary, treatment evoked, increase serum IgM level, was decreased in the Ibr+R arm compared to the Pbo+R arm: 8.0% vs. 46.7%, respectively.

Of the 1,200 subjects treated with ibrutinib for CLL, WM, or MCL comprising the Overall Label Pool, 5.1% discontinued treatment primarily due to ADRs. These included pneumonia, atrial fibrillation, hemorrhage, and thrombocytopenia. Adverse drug reactions leading to dose reduction occurred in 6.6% of the 1,200 subjects.

Based on the new safety information from Studies 1130 and 1127, no new ADRs were identified for ibrutinib and the frequencies of reported ADRs were similar to those reported in the currently approved SmPC. Warnings regarding hypertension have been included in section 4.4 to recommend regular monitoring of blood pressure in patients treated with Imbruvica and initiation or adjustment of

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antihypertensive medication throughout treatment as appropriate.

2.5.2. Conclusions on clinical safety

The safety profile of ibrutinib in patients with WM is overall consistent with what is already known in ibrutinib treated patients with CLL/SLL and MCL. No new safety signal has been seen. A higher frequency of hypertension was noted and also seen to increase in a time-on treatment-dependent way. The SmPC has been updated accordingly.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.0 is acceptable. The PRAC advice is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.0 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Leukostasis Haemorrhage Tumour lysis syndrome Hepatotoxicity (including hepatic failure) Non-melanoma skin cancer Interstitial lung disease (ILD) Atrial fibrillation <u>Hypertension</u>
Important potential risks	Drug-drug interaction Anaemia Neutropenia Thrombocytopenia Progressive multifocal leukoencephalopathy (PML) Infections (including viral reactivation) Cardiac arrhythmia (including ventricular tachyarrhythmia) Severe GI disorders Other malignancies (excluding non-melanoma skin cancer) Hypersensitivity Teratogenicity Eye disorders

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Summary of safety concerns	
	Renal failure ~~Hypertension~~
Missing information	Use in paediatric patients Use in breastfeeding Use in patients with severe cardiac disease Use in patients with severe renal impairment Use in patients with severe hepatic impairment Long-term use (>2 years)

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
PCYC-1112-CA the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Ongoing	Yearly updates of trial results for progression and death.	Overall safety profile	Primary analysis	1st Quarter 2014: completed
			Yearly updates	2nd Quarter 2015: completed
				2nd Quarter 2016: completed
				2nd Quarter 2017: completed
				2nd Quarter 2018: completed
				2nd Quarter 2019 (Final report)
Category 3 - Required additional pharmacovigilance activities				
54179060NAP4001 Enhanced pharmacovigilance to evaluate the risks of hemorrhage with the administration of IMBRUVICA® (ibrutinib): A	To study the risk of serious bleeding from clinical trials and all postmarketing sources	Hemorrhage	Final report	4th Quarter 2018

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Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
post-marketing requirementAdditional Pharmacovigilance Study to Evaluate the Risks of Major Hemorrhage With the Administration of IMBRUVICA® (ibrutinib) Ongoing				
PCI-32765MCL3002 A randomized, double-blind, placebo-controlled Phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab (BR) in subjects with newly diagnosed mantle cell lymphoma Ongoing	Evaluate efficacy and safety of ibrutinib in combination with BR versus BR alone	Overall safety profile	Final report	3rd Quarter 2020
54179060CLL1017 A Drug-Drug Interaction Study to Evaluate the Effect of Ibrutinib on the Pharmacokinetics of Oral Contraceptives, CYP2B6, and CYP3A4 Substrates in Female Subjects with B-cell Malignancy Ongoing	Determine the effect of ibrutinib on the exposure of oral contraceptives	Drug-drug interaction	Final report	2nd Quarter 2020

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Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-term Safety Study 3038-1 Ongoing	To assess long-term safety of ibrutinib	Long-term use (>2 years) Non-melanoma skin cancer Other malignancies (excluding non-melanoma skin cancer)	Year 4 – Interim report Year 5 – Final report	2nd Quarter 2018: completed 2nd Quarter 2019

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Activities
Leukostasis	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations regarding management of patients experiencing leukostasis is provided in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Haemorrhage	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning not to use warfarin or other vitamin K antagonists concomitantly with ibrutinib, to avoid supplements such as fish oil and vitamin E, advice on use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function, and advice on use pre- and post-surgery is provided in SmPC Section 4.4 • Warning for patients with prior unusual bruising or bleeding and advice

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Safety Concern	Routine Risk Minimisation Activities
	on concomitant use of medicines that increase the risk of bleeding is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Tumour lysis syndrome	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations regarding management of patients experiencing tumour lysis syndrome is provided in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Hepatotoxicity (including hepatic failure)	Routine risk communication: SmPC Section 4.8 SmPC Section 4.9 PL Section 2 PL Section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Non-melanoma skin cancer	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Interstitial lung disease (ILD)	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Routine risk minimisation activities recommending specific clinical

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Safety Concern	Routine Risk Minimisation Activities
	measures to address the risk: • Recommendations regarding management of patients developing symptoms that are consistent with ILD (including treatment interruption) is provided in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Atrial fibrillation	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations regarding management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib, is provided in SmPC Section 4.4 • Advice for patients experiencing (a history of) irregular heart beat is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Hypertension	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations regarding blood pressure monitoring and management of patients with hypertension are provided in SmPC Section 4.4 Advice for patients having high blood pressure is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Drug-drug interaction	Routine risk communication: SmPC Section 4.2 SmPC Section 4.3

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Safety Concern	Routine Risk Minimisation Activities
	SmPC Section 4.4 SmPC Section 4.5 SmPC Section 5.2 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations regarding management of patients concomitantly using moderate or strong CYP3A4 inhibitors (dosage reduction or treatment interruption) is provided in SmPC Section 4.2 • Recommendations regarding management of patients concomitantly using strong or moderate CYP3A4 inhibitors/inducers (use to be avoided when possible) are provided in SmPC Section 4.4 • Recommendations regarding use of concomitant drug that may change ibrutinib plasma concentrations are provided in SmPC Section 4.5 • Advice for patients taking other medicines is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Anaemia	Routine risk communication: SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Neutropenia	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Thrombocytopenia	Routine risk communication: SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription

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Safety Concern	Routine Risk Minimisation Activities
Progressive multifocal leukoencephalopathy (PML)	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations regarding management of patients with suspected PML are provided in SmPC Section 4.4 • Signs and symptoms of PML are provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Infections (including viral reactivation)	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Preventive measures and management regarding hepatitis B reactivation are provided in SmPC Section 4.4 • Warning for patients who had or have a hepatitis B infection is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Cardiac arrhythmia (including ventricular tachyarrhythmia)	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations regarding management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) is provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2

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Safety Concern	Routine Risk Minimisation Activities
	Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Severe GI disorders	Routine risk communication: SmPC Section 4.8 PL Section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Other malignancies (excluding non-melanoma skin cancer)	Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Hypersensitivity	Routine risk communication: SmPC Section 4.3 SmPC Section 4.8 PL Section 2 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • A list of excipients is provided in SmPC Section 6.1 and PL Section 6 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Teratogenicity	Routine risk communication: SmPC Section 4.4 SmPC Section 4.6 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation regarding the use of ibrutinib during pregnancy, and use of contraception is provided in SmPC Sections 4.4 and 4.6 and PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Eye disorders	Routine risk communication: • SmPC Section 4.8 • PL Section 4

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Safety Concern	Routine Risk Minimisation Activities
	Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Renal failure	Routine risk communication: • SmPC Section 4.2 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Advice for patients having kidney problems is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Hypertension	Routine risk communication: SmPC Section 4.8 PL Section 4 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Severe cutaneous adverse reactions	Routine risk communication: SmPC Section 4.8 PL Section 4 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Use in paediatric patients	Routine risk communication: SmPC Section 4.2 SmPC Section 5.1 PL Section 2 PL Section 5 Other routine risk minimisation measures beyond the Product Information Warning to keep the product out of the sight and reach of children Legal status: restricted medical prescription
Use during breastfeeding	Routine risk communication: SmPC Section 4.6 PL Section 2 Routine risk minimisation activities recommending specific clinical

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Safety Concern	Routine Risk Minimisation Activities
	measures to address the risk: • Recommendation regarding the use of ibrutinib during breastfeeding is provided in SmPC Section 4.6 and PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Use in patients with severe cardiac disease	Routine risk communication: • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations regarding management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) is provided in SmPC Section 4.4 • Recommendations regarding management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib, is provided in SmPC Section 4.4 • Warning for patients having severe heart failure is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Use in patients with severe renal impairment	Routine risk communication: SmPC Section 4.2 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Advice for patients having kidney problems is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription

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Safety Concern	Routine Risk Minimisation Activities
Use in patients with severe hepatic impairment	Routine risk communication: SmPC Section 4.2 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation regarding management of patients with mild, moderate, or severe hepatic impairment is provided in SmPC Section 4.2 • Advice for patients having liver problems is provided in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Long-term use (>2 years)	Routine risk communication: SmPC Section 4.8 Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4,4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to hypertension has been added to the product information.

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab.

3.1.2. Available therapies and unmet medical need

In the EU, only a minority of patients are offered monotherapy rituximab for the treatment of WM according to a recent large retrospective chart review (Lancet Haematol 2018, C Buske et al). Data from Medicare claims linked to Surveillance, Epidemiology and End Results (SEER) data, which evaluated changes in the presentation, management, and survival among 2,666 Medicare beneficiaries, diagnosed

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with WM between 1994 and 2011 in the US – show that rituximab monotherapy was prescribed for >50% of patients since 2004, and combination CIT for a further 30%. Based on input from the WM Consortium Group and a Joint CHMP-HTA Scientific Advice in 2014 regarding the design of Study 1127, the importance of a treatment of WM to move toward to a chemotherapy-free regimen, to control the disease and improve quality of life, is underlined.

3.1.3. Main clinical studies

Study 1127 is a Phase 3, randomized, double-blind, placebo-controlled, multicentre study with the aim to evaluate the efficacy and safety of ibrutinib in combination with rituximab versus rituximab alone in subjects 18 years of age or older with untreated or previously treated WM. In addition, an open-label substudy (Treatment Arm C) was included to further investigate the efficacy and safety of ibrutinib as a monotherapy in adult subjects with WM who were considered refractory to the last prior rituximab-containing therapy.

A total of 150 subjects were included in the randomised part (75 patients in each arm) and 31 subjects were included in the monotherapy sub-study. Primary endpoint was progression-free survival (PFS) in the experimental arm, Ibr+R, compared to placebo Pbo+R, in subjects with WM. The study design was developed considering the scientific advice from regulatory agencies, including CHMP in 2014.

3.2. Favourable effects

The study met its primary endpoint with an improvement of median PFS (IRC assessed). Median PFS was not reached for the Ibr+R arm and was 20.3 months for the Pbo+R arm (HR = 0.202 (95% CI: 0.107, 0.380), $p < 0.0001$). The Kaplan-Meier point estimates of the PFS rate at 30 months were 82 % for the Ibr+R arm and 28 % for the Pbo+R arm.

The sensitivity analyses performed on PFS supports the result in the primary analysis and the treatment effect was consistent across the pre-specified subgroups. The benefit in the Ibr+R group over that in the Pbo+R group was independent of the MYD88 or CXCR4 genotype. The secondary endpoint, RR (≥ PR) per IRC assessment was significantly higher for the Ibr+R arm than the Pbo+R arm: 72.0% Ibr+R vs. 32.0% Pbo+R, rate ratio = 2.299 (95% CI: 1.592; 3.319), $p < 0.0001$. In terms of TTnT, median TTnT showed a statistically significant advantage for the Ibr+R arm; it was not reached for the Ibr+R arm and it was 18.1 months (95% CI: 11.1, NE) for the Pbo+R arm, HR = 0.096 (95% CI: 0.040, 0.227), $p < 0.0001$. At the 30-month landmark time point an estimated 91.5% of subjects in the Ibr+R arm and 41.4% of subjects in the Pbo+R arm had not received subsequent treatment. Any subsequent antineoplastic therapy was received by 6 subjects (8.0%) in the Ibr+R arm and 41 subjects (54.7%) in the Pbo+R arm, of which 30 subjects received ibrutinib as crossover therapy. The median OS was not reached for either treatment arm. There were 4 deaths in the Ibr+R arm and 6 deaths in the Pbo+R arm. In terms of HQoL/ EQ-5D-5L PRO results compliance was high (≥ 90%) and showed similar results for patients in both arms for whom data was available.

Study 1127 demonstrated a statistically significant improvement with Ibr+R treatment compared with Pbo+R when evaluating sustained Hgb improvement for subjects with untreated or previously treated WM. A substantial improvement of Hgb was also seen in the monotherapy substudy arm. In study 1118E the Hgb improvement was lower than seen in the single arm substudy of 1127.

In terms of clinical response rate (≥ MR), the rate was comparable between the two monotherapy arms (substudy 1127 and 1118E) and Ibr+R, 87 %, 83 % and 92 % respectively.

Infusion reactions was recorded for a substantially fewer subjects in the Ibr+R arm compared to the Pbo+R arm, 1.3 % versus 16 %. Thus Ibrutinib sees clearly to be protective against infusion reactions

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caused by rituximab.

3.3. Uncertainties and limitations about favourable effects

It was also clarified that the time point for data cut-off was the same as the extraction of data, i.e. 12 Oct 2017. The maturation of PFS data presently presented is, in the Pbo+R arm 56 % versus 18.7 % in the Ibr+R. Updated efficacy results and PFS2 data will, according to the applicant, be presented at the time of the final analysis of study 1127, which is planned to take place by the end of June 2020. At this time, it will be possible to evaluate possible impaired effect on response to CIT (next line of therapy) upon progression on ibrutinib treatment.

The role of rituximab is unclear in the combination arm, since the isolation of ibrutinib and the potential effect of adding rituximab is impossible to disentangle in the presented data. Cross study comparisons with previous monotherapy study 1118E and the ibrutinib monotherapy substudy in the present study 1127, are not indicative of additive effect. However, rituximab it is a well-recognized treatment option due to its established monotherapy activity as well as a synergistic effect when combined with chemotherapy. Therefor the add-on strategy is deemed acceptable, from a regulatory perspective.

3.4. Unfavourable effects

Overall tolerability of ibrutinib given in combination with rituximab is consistent with its known safety profile. Safety data from study 1127 is also put in the context of the Current label pool for ibrutinib, consisting of 981 subjects (both monotherapy and various combination treatment data).

In summary, the most common adverse events of any grade with ibrutinib-rituximab included infusion-related reactions, diarrhea, arthralgia, and nausea. Events of grade ≥ 3 that occurred more frequently with ibrutinib-rituximab than with placebo-rituximab included atrial fibrillation (12% vs. 1%) and hypertension (13% vs. 4%); those that occurred less frequently included infusion reactions (1% vs. 16%) and any grade of IgM flare (8% vs. 47%). The major hemorrhage rate was the same in the two trial groups (4%). Hypertension was observed to increase in prevalence with time on continued ibrutinib treatment, which is reflected in the PI ; hypertension is an important identified risk of ibrutinib and the RMP was updated accordingly.

3.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties in the assessment of safety.

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3.6. Effects Table

Table 36: Effects Table for ibrutinib for the treatment of Waldenström Macroglobulinemia (iNNOVATE, PCYC-1127, data cut-off: 12 Oct 2017)

Effect	Short Description	Unit	Treatment Ibrutinib + rituximab (n=75)	Control Placebo + rituximab (n=75)	Mono-therapy substudy (n=31)	Uncertainties Strength of evidence / Comment
Favourable Effects			**Study 1127 (ITT) Randomised part**		**Study 1127 (All treated) Single agent**	
Primary endpoint						
PFS (IRC)	months(median,95% CI)		NE (35.0, NE)	20.3(13.7, 27.6)	NE (27.4, NE)	
	p-value HR(95% CI)		<0,0001 0. 202 (0.107, 0.380)		N/A	
Number of events	%		18.7	56		
Key secondary endpoints						
RR (IRC) (≥ partial response, PR)	%		72.0	32.0	71	
	p-value HR(95% CI)		<0.0001 2. 299 (1.592, 3.319)		N/A N/A	
TTnT	Months		NE (NE, NE)	18.1 (11.1, NE)	NE (NE, NE)	
	p-value HR(95% CI)		<0.0001 0.096 (0.040, 0.227)		N/A N/A	
Sustained Hgb, by week 25 All subjects	%		73.3	41.3	71.0	
	p-value rate ratio(95% CI)		<0.0001 1. 705 (1.322, 2.197)			
OS	months Median 95% CI		NE (NE, NE)	NE (NE, NE)		Data immature
Unfavourable Effects						
≥ 1 TEAE		%	100	100	97	
TEAE grade ≥3		%	60	61	74	
SAE		%	43	33	36	
TEAE leading to dose reduction		%	19	0		
TEAE leading to dose discontinuation		%	5	7	7	
Deaths due to TEAEs		%	0	4	0	

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3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on the findings in a Phase 2 study in WM, 1118E, ibrutinib monotherapy has shown clinically relevant benefit in WM subjects who had failed prior CD20 therapy (either alone or in combination with other agents). This supported a second line indication in WM, also including those patients being unfit for CIT as first line therapy. The results from the randomized part of, Study 1127 with a median time on study of 26.5 months (both arms) demonstrate that treatment with combination of Ibr+R results in clinically meaningful and statistically significant improvement of PFS, response rates, DOR and sustained Hgb improvements compared with Pbo+R treatment. This was shown in subjects that were both treatment-naïve and previously treated WM.

The results also demonstrate a significantly longer time to next line of WM therapy (TTnT) as well as lower rates of infusion reactions in the Ibr+R-treated subjects compared with Pbo+R-treated subjects. The treatment effect of Ibr+R on PFS was robust and consistent across all predefined subgroups.

For the 1127 open-label monotherapy substudy (Treatment Arm C), enrolling only subjects considered refractory to the last prior rituximab-containing therapy, the efficacy results (after a median time on study of 34.4 months) for PFS, response rates and sustained Hgb improvements, further confirm the efficacy of single agent ibrutinib, as previously observed in Study 1118E, for the treatment of WM.

No new safety signals were observed; the majority of the TEAE rates are essentially consistent with the known safety profile in the current label pool. In summary, the safety profile for ibrutinib is in large consistent with its known safety profile. The risks known to be associated with the use of ibrutinib (e.g. hemorrhage, neutropenia, infections, arthralgia) are manageable through medical management with routine clinical assessment. This also accounts for the known TEAEs like atrial fibrillation and hypertension.

3.7.2. Balance of benefits and risks

Data from the primary analysis from the study 1127 in WM, showed superiority on PFS of the combination of Ibr+R over Pbo+R, in treatment-naïve and previously treated patients WM. Furthermore, the results from the ibrutinib monotherapy substudy in rituximab-refractory patients indicate a treatment effect comparable to the results in the ibrutinib-containing arm in the randomised study. Furthermore, Study 1127 investigated the "add on" of ibrutinib or placebo to rituximab in a population with both treatment-naïve patients and previously treated patients.

The MAH is encouraged to further investigate the efficacy of ibrutinib + rituximab *vs* ibrutinib monotherapy in the broad indication WM.

In order to better understand the ibrutinib resistance, there is need of PFS2 data or a corresponding proxy such as time to second subsequent therapy. The MAH will provide final results in June 2020 were also PFS2 data will be presented (see RMP).

3.8. Conclusions

The overall B/R of Imbruvica in the treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab is positive.

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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 to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab; as a consequence, section 4.1 and 4.8 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) was agreed.

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

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 to include treatment of adult patients with Waldenström's macroglobulinaemia (WM) in combination with rituximab; as a consequence, section 4.1 and 4.8 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) was agreed.

Summary

Please refer to Scientific Discussion Imbruvica–H-C-3791-II-0046.

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